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Application for Extension of Patent Term

IN RE: U.S. Patent No. 7,230,098

ISSUED: JUNE 12, 2007

TO: JINGRONG JEAN CUI, ET.AL.

FOR: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

FROM: Serial No. 10/786,610

FILING DATE: February 26, 2004

ORIGINAL

PC23572A
Transmittal Letter for the Application for Extension of
Patent Term under 35 U.S.C. §156
From Serial No. 10/786,610

9/16-11

Certificate of Mailing (37 C.F.R. §1.10):

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail (**EV 615409756 US**) in an Express Mail Box addressed to: **Mail Stop: Hatch-Waxman PTE**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this **14th** day of **September** 2011.

s/ Christina M. Compelube
Christina M. Compelube

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 7,230,098

ISSUED: JUNE 12, 2007

TO: JINGRONG JEAN CUI, ET.AL.

FOR: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

FROM: Serial No. 10/786,610

FILING DATE: February 26, 2004

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Transmitted herewith is the Application of Pfizer Inc. for extension of the term of United States Patent No. 7,230,098, under 35 U.S.C. §156, together with exhibits and copies thereof.

Pursuant to 37 C.F.R. §1.20(j)(1), please charge Deposit Account No. 16-1445 the amount of $1,120.00 for the filing of the instant Application. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Two copies of this paper are enclosed.

Respectfully submitted,

Vincent P. Liptak
Attorney for Applicant
Reg. No. 53,225

Date: September 14, 2011
PFIZER INC
Patent Department
10555 Science Center Dr.
San Diego, CA 92121
(858) 622-7908

PC23572A
Transmittal Letter Listing Contents of PTE Application
for United States Patent No. 7,230,098
From Serial No. 10/786,610

Certificate of Mailing (37 C.F.R. §1.10):

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s/
Christina M. Compelube

OPAP SEP 14 2011 PATENT & TRADEMARK OFFICE

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CANCELLED

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 7,230,098

ISSUED: JUNE 12, 2007

TO: JINGRONG JEAN CUI, ET AL.

FOR: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

FROM: Serial No. 10/786,610

FILING DATE: February 26, 2004

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Transmitted herewith are the following documents:

1.	Application for Extension of Patent Term Transmittal	1 Page;
2.	Application for Extension of United States Patent No. 7,230,098	22 Pages;
	a. Exhibit A	624 Pages,
	b. Exhibit B	1 Page,
	c. Exhibit C	4 Pages,
	d. Exhibit D	32 Pages,
	e. Exhibit E	19 Pages,
	Total Application =	**703 Pages**
3.	Two Copies of Complete Application	1,406 Pages in Total;
4.	Return Postcard	1 Postcard; and
5.	Total Fee Due of $1,120.00	Deposit Account.

Respectfully submitted,

Date: September 14, 2011

Vincent P. Liptak
Attorney for Applicants
Registration No. 53,225

Pfizer Inc.
Patent Department
10555 Science Center Drive
San Diego, California 92121
Phone: (858) 622-7908

Certificate of Mailing (37 C.F.R. §1.10):

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail (**EV 615409756 US**) in an Express Mail Box addressed to: **Mail Stop: Hatch-Waxman PTE**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this **14th** day of **September** 2011.

s/ CMC
Christina M. Compelube

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 7,230,098

ISSUED: JUNE 12, 2007

TO: JINGRONG JEAN CUI, ET AL.

FOR: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

FROM: Serial No. 10/786,610

FILING DATE: February 26, 2004

Commissioner for Patents
P.O. Box 1450
Mail Stop: Hatch-Waxman PTE
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF UNITED STATES PATENT NO. 7,230,098 UNDER 35 U.S.C. §156

Sir:

Applicant, PFIZER INC. ("PFIZER"), a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, NY 10017, represents that it is the owner of the entire right, title, and interest in and to, Letters Patent of the United States No. 7,230,098 granted to JINGRONG JEAN CUI, DILIP BHUMRALKAR, IRINY BOTROUS, JI YU CHU, LEE A. FUNK, CATHLEEN ELIZABETH HANAU, G. DAVIS HARRIS, LEI JIA, JOANNE JOHNSON, STEPHEN A. KOLODZIEJ, PEI-PEI KUNG, XIAOYUAN (SHARON) LI, JASON (QISHEN) LIN, JERRY JIALUN MENG, MITCHELL DAVID NAMBU, CHRISTOPHER G. NELSON, MASON ALAN PAIRISH, HONG SHEN, MICHELLE TRAN-DUBE, ALLISON WALTER, FANG-JIE ZHANG, and JENNIFER ZHANG on the 12th day of June, 2007, for "AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS", by virtue of the following:

On July 1, 2004, JINGRONG JEAN CUI assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 1, 2004, DILIP BHUMRALKAR assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 8, 2004, IRINY BOTROUS assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 2, 2004, JI YU CHU assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 2, 2004, LEE A. FUNK assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 1, 2004, CATHLEEN ELIZABETH HANAU assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 15, 2004, G. DAVIS HARRIS assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and

all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 2, 2004, LEI JIA assigned, *inter alia,* all of her right, title and interest in, and to, U.S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 1, 2004, JOANNE JOHNSON assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On June 30, 2004, STEPHEN A. KOLODZIEJ assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 2, 2004, PEI-PEI KUNG assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 7, 2004, XIAOYUAN (SHARON) LI assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 9, 2004, JASON (QISHEN) LIN assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which

assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On June 30, 2004, JERRY JIALUN MENG assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 9, 2004, MITCHELL DAVID NAMBU assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 15, 2004, CHRISTOPHER G. NELSON assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 9, 2004, MASON ALAN PAIRISH assigned, *inter alia,* all of his right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 1, 2004, HONG SHEN assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On June 29, 2004, MICHELLE TRAN-DUBE assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which

assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 9, 2004, ALLISON WALTER assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 1, 2004, FANG-JIE ZHANG assigned, *inter alia,* all of her right, title and interest in, and to, U. S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On July 7, 2004, JENNIFER ZHANG assigned, *inter alia,* all of her right, title and interest in, and to, U.S. Patent Application Serial No. 10/786,610, filed February 26, 2004 and all United States Letters Patent which may be granted therefor to SUGEN INC., which assignment was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

Whereas by virtue of the terms of employment of Jingrong Jean Cui, Dilip Bhumralkar, Iriny Botrous, Lee A. Funk, Lei Jia, Pei-Pei Kung, Jason (Qishen) Lin, Jerry Jialun Meng, Mitchell David Nambu, Christopher G. Nelson, Mason Alan Pairish, Hong Shen, and Michelle Tran-Dube with PFIZER, PFIZER was entitled to an assignment of the invention described in U.S. Patent Application Serial No. 10/786,610. Full benefit of the assignment by these inventors was granted to SUGEN, INC. by virtue of CONSENT OF PFIZER INC., which consent was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

Whereas by virtue of the terms of employment of Cathleen Elizabeth Hanau and Stephen A. Kolodziej with PHARMACIA & UPJOHN CORPORATION ("PHARMACIA"), PHARMACIA was entitled to an assignment of the invention described in U.S. Patent Application Serial No. 10/786,610. Full benefit of the assignment by these inventors was granted to SUGEN INC. by virtue of CONSENT OF PHARMACIA & UPJOHN CORPORATION,

which consent was recorded in the United States Patent and Trademark Office on July 19, 2004 at Reel 014867, Frame 0434.

On May 31, 2011, SUGEN INC. assigned, *inter alia*, all of its right, title and interest in, and to, U.S. Patent Application Serial No. 10/786,610, filed February 26, 2004 which granted as United States Patent Number 7,230,098 on June 12, 2007 to PFIZER INC., which assignment was recorded in the United States Patent and Trademark Office on June 1, 2011 at Reel 026373, Frame 0485.

Pursuant to the provisions of 37 C.F.R. §1.730, Applicant hereby applies for an extension of the term of said United States Patent No. 7,230,098 of 178 days under 35 U.S.C. §156 based on the materials and accompanying papers set forth herein. In the materials following herein, paragraphs numbered "1" through "15" correspond to paragraph numbers "1" through "15" in 37 C.F.R. §1.740(a).

(1) The approved product is Xalkori™, further identified as follows:

Chemical Names

(R)-3-[(1-(2,6-Dichloro-3-fluorophenyl)ethoxy)]-5-[(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)]pyridin-2-amine

CAS Registry Number

877399-52-5

Generic Name

crizotinib

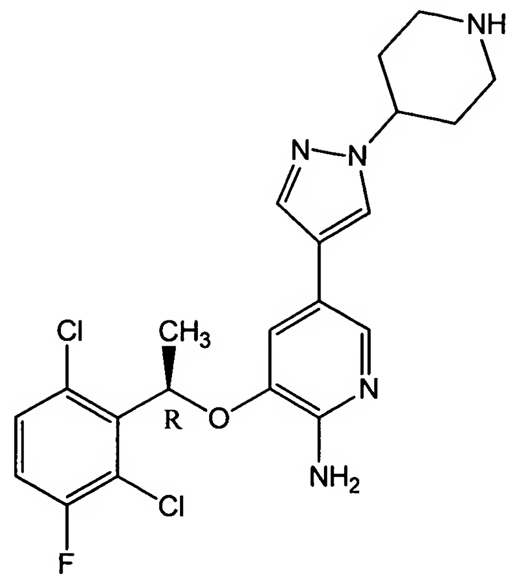
Molecular Formula

$C_{21}H_{22}Cl_2FN_5O$

Molecular Weight

450.34

Chemical Structure



Physical Characteristics

Crizotinib exists as a powder when recrystallized from isopropanol, m.p. 195°C. It is water-soluble to 0.034 mg/ml. Absorption max: 322 nm.

(2) Xalkori™ was subject to regulatory review under §505 (b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355 (b)).

(3) Xalkori™ received permission for commercial marketing or use under §505 (b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(b)) on August 26, 2011.

(4) The active ingredient in Xalkori™ is crizotinib, as the free base, which ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This Application is being submitted within the sixty-day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this Application could be submitted is October 24, 2011.

(6) The patent for which an extension is being sought is identified as follows:
Inventors: JINGRONG JEAN CUI, DILIP BHUMRALKAR, IRINY BOTROUS, JI YU CHU, LEE A. FUNK, CATHLEEN ELIZABETH HANAU, G. DAVIS HARRIS, LEI JIA, JOANNE JOHNSON, STEPHEN A. KOLODZIEJ, PEI-PEI KUNG, XIAOYUAN (SHARON) LI, JASON (QISHEN) LIN, JERRY JIALUN MENG, MITCHELL DAVID NAMBU,

CHRISTOPHER G. NELSON, MASON ALAN PAIRISH, HONG SHEN, MICHELLE TRAN-DUBE, ALLISON WALTER, FANG-JIE ZHANG, and JENNIFER ZHANG

U.S. Patent No.: 7,230,098

Title: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

Issued: June 12, 2007

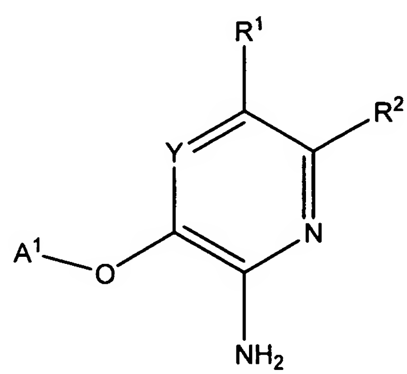
Expires: March 1, 2025. The normal expiration date of U.S. Patent No. 7,230,098 ("the 098 patent") is February 26, 2024, which is 20 years from the date on which the application for the patent was filed in the United States, which was February 26, 2004. The '098 patent received 369 days of patent term adjustment (PTA) under 35 U.S.C 154(b) resulting in a PTA extended expiration date of March 1, 2025.

(7) A copy of U.S. Patent No. 7,230,098, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) One receipt for a maintenance fee payment has issued for this patent, a copy of which is attached hereto as EXHIBIT B. One copy of a Request for Certificate of Correction, filed on September 8, 2011, is attached hereto as EXHIBIT C.

(9) U.S. Patent No. 7,230,098 claims the approved product. Claims 1 through 14, inclusive, claim the approved product. The manner in which each applicable claim reads on the approved product is as follows.

Claim 1 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 1



1

or a pharmaceutically acceptable salt or hydrate thereof, in which

Y is CR^{12};

R^1 is selected from C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, $-S(O)_mR^4$, $-SO_2NR^4R^5$, $-S(O)_2OR^4$, $-NO_2$, $-NR^4R^5$, $-(CR^6R^7)_nOR^4$, -CN, $-C(O)R^4$, $-OC(O)R^4$, $-O(CR^6R^7)_nR^4$, $-NR^4C(O)R^5$, $-(CR^6R^7)_nC(O)OR^4$, $-(CR^6R^7)_nNCR^4R^5$, $-C(=NR^6)NR^4R^5$, $-NR^4C(O)NR^5R^6$, $-NR^4S(O)_pR^5$ or $-C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl, or 3-12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5-12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic or 5-12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -CN, $-O-C_{1-12}$ alkyl, $-O-(CH_2)_nC_{3-12}$ cycloalkyl, $-O-(CH_2)_nC_{6-12}$ aryl, $-O-(CH_2)_n$(3-12 membered heteroalicyclic) or $-O-(CH_2)_n$(5-12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is $-(CR^9R^{10})_n-A^2$

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, $-S(O)_mR^4$, $-SO_2NR^4R^5$, $-S(O)_2OR^4$, $-NO_2$, $-NR^4R^5$, $-(CR^6R^7)_nOR^4$, -CN, $-C(O)R^4$, $-OC(O)R^4$, $-NR^4C(O)R^5$, $-(CR^6R^7)_nC(O)OR^4$, $-(CR^6R^7)_nNCR^4R^5$, $-NR^4C(O)NR^5R^6$, $-NR^4S(O)_pR^5$ or $-C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic, C_{6-12} aryl or 5-12

membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl or 3-12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -O-C_{1-12} alkyl, -O-$(CH_2)_nC_{3-12}$ cycloalkyl, -O-$(CH_2)_nC_{6-12}$ aryl, -O-$(CH_2)_n$(3-12 membered heteroalicyclic), -O-$(CH_2)_n$(5-12 membered heteroaryl) or -CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, -OH, -CN, -C_{1-12} alkyl which may be partially or fully halogenated, -O-C_{1-12} alkyl which may be partially or fully halogenated, -CO, -SO and -SO_2;

R^{12} is hydrogen;

m is 0, 1 or 2;

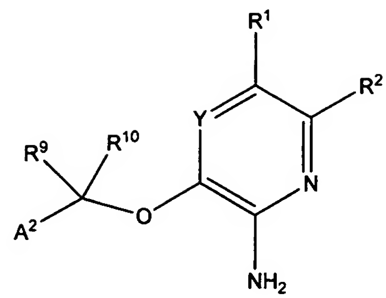
n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

wherein said 3-12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5-12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine.

When R^1 is a 5-12 membered heteroaryl substituted by one R^3 group (where 5-12 membered heteroaryl is pyrazole, R^3 is 3-12 membered heteroalicyclic, and 3-12 membered heteroalicyclic is piperidine), A^1 is $-(CR^9R^{10})_n$-A^2, one of R^9 or R^{10} is C_{1-12} alkyl, the other of R^9 or R^{10} is hydrogen, A^2 is C_{6-12} aryl substituted by three R^3 groups that are each halogen, R^{12} is H and n is 1, the compound of the formula 1 embraces crizotinib. Therefore, claim 1 reads on the approved product.

<u>Claim 2</u> of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 1a



1a

in which the definition of Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, m, n and p are the same as in claim 1, but the definition of A^2 is restricted. In the restricted definition, A^2 can be C_{6-12} aryl or 5-12 membered heteroaryl optionally substituted by one or more R^3 groups. Thus, when A^2 is C_{6-12} aryl substituted by three R^3 groups that are each halogen, claim 2 embraces crizotinib and reads on the approved product.

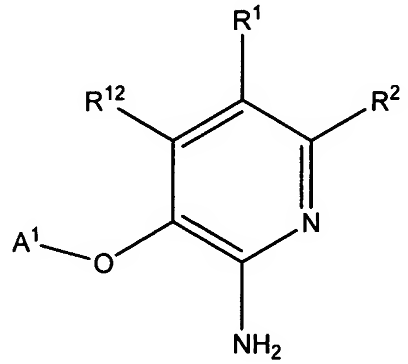
Claim 3 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 1a in which the definition of Y, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, A^2, m, n and p have the same definition as in claim 2, but the definition of R^1 is restricted. In the restricted definition, R^1 is selected from C_{6-12} aryl and 5-12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. Thus, when R^1 is 5-12 membered heteroaryl having one hydrogen substituted by one R^3 group, claim 3 embraces crizotinib and reads on the approved product.

Claim 4 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 1a in which the definition of Y, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, m, n and p are the same as in claim 2, but the definition of A^2 is restricted. In the restricted definition, A^2 is substituted by at least one halogen atom. Therefore, claim 4 embraces crizotinib and reads on the approved product.

Claim 5 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 1 in which the definition of Y, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, A^1, A^2, m, n, p are the same as in claim 1, but the definition of R^1 is restricted. In the restricted definition, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. Thus, when R^1 is

pyrazole substituted by one R^3 group, claim 5 embraces crizotinib and reads on the approved product.

Claim 6 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 2



2

or a pharmaceutically acceptable salt or hydrate thereof, in which

R^1 is selected from C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, $-S(O)_mR^4$, $-SO_2NR^4R^5$, $-S(O)_2OR^4$, $-NO_2$, $-NR^4R^5$, $-(CR^6R^7)_nOR^4$, -CN, $-C(O)R^4$, $-OC(O)R^4$, $-O(CR^6R^7)_nR^4$, $-NR^4C(O)R^5$, $-(CR^6R^7)_nC(O)OR^4$, $-(CR^6R^7)_nNCR^4R^5$, $-C(=NR^6)NR^4R^5$, $-NR^4C(O)NR^5R^6$, $-NR^4S(O)_pR^5$ or $-C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl or 3-12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5-12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic or 5-12

membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -CN, -O-C_{1-12} alkyl, -O-$(CH_2)_n C_{3-12}$ cycloalkyl, -O-$(CH_2)_n C_{6-12}$ aryl, -O-$(CH_2)_n$(3-12 membered heteroalicyclic) or -O-$(CH_2)_n$(5-12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is –$(CR^9R^{10})_n$-A^2;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -$S(O)_mR^4$, -$SO_2NR^4R^5$, -$S(O)_2OR^4$, -NO_2, –NR^4R^5, -$(CR^6R^7)_nOR^4$, -CN, -$C(O)R^4$, -$OC(O)R^4$, -$NR^4C(O)R^5$, -$(CR^6R^7)_nC(O)OR^4$, -$(CR^6R^7)_nNCR^4R^5$, -$NR^4C(O)NR^5R^6$, -$NR^4S(O)_pR^5$ or -$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic, C_{6-12} aryl or 5-12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl or 3-12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -O-C_{1-12} alkyl, -O-$(CH_2)_n C_{3-12}$ cycloalkyl, -O-$(CH_2)_n C_{6-12}$ aryl, -O-$(CH_2)_n$(3-12 membered heteroalicyclic), -O-$(CH_2)_n$(5-12 membered heteroaryl) or -CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, -OH, -CN, -C_{1-12} alkyl which may be partially or fully halogenated, -O-C_{1-12} alkyl which may be partially or fully halogenated, -CO, -SO and -SO_2;

R^{12} is hydrogen;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

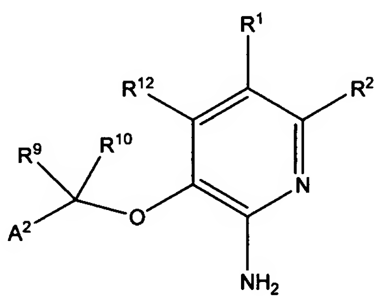
p is 1 or 2;

wherein said 3-12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5-12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole,

pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine.

When R^1 is a 5-12 membered heteroaryl substituted by one R^3 (where 5-12 membered heteroaryl is pyrazole, R^3 is 3-12 membered heteroalicyclic, and 3-12 membered heteroalicyclic is piperidine), R^2 is H, A^1 is $-(CR^9R^{10})_n-A^2$, one of R^9 or R^{10} is C_{1-12} alkyl, the other of R^9 or R^{10} is hydrogen, A^2 is C_{6-12} aryl substituted by three R^3 groups that are each halogen, R^{12} is H and n is 1, the compound of the formula 2 embraces crizotinib. Therefore, claim 6 reads on the approved product.

Claim 7 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 2a



2a

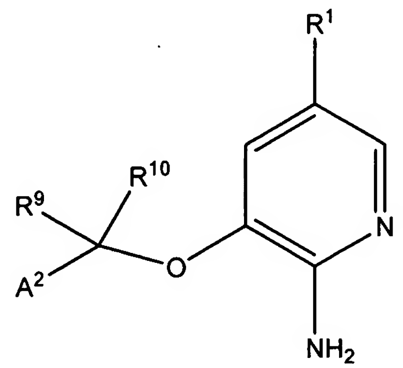
in which the definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, m, n and p are the same as in claim 6, but the definition of A^2 is restricted. In the restricted definition, A^2 can be C_{6-12} aryl or 5-12 membered heteroaryl optionally substituted by one or more R^3 groups. Thus when A^2 is C_{6-12} aryl substituted by three R^3 groups that are each halogen, claim 7 embraces crizotinib and reads on the approved product.

Claim 8 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 2a in which the definition of R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, A^2, m, n and p have the same definition as in claim 7, but the definition of R^1 is restricted. In the restricted definition, R^1 is selected from C_{6-12} aryl and 5-12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. Thus, when R^1 is a 5-12 membered heteroaryl substituted by one R^3 group, claim 8 embraces crizotinib and reads on the approved product.

Claim 9 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 2a in which the definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, m, n and p are the same as in claim 7, but the definition of A^2 is restricted. In the restricted definition, A^2 is substituted by at least one halogen atom. Therefore, claim 9 embraces crizotinib and reads on the approved product.

Claim 10 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 2a in which the definition of Y, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, A^1, A^2, m, n, p are the same as in claim 6, but the definition of R^1 is restricted. In the restricted definition, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. Thus, when R^1 is pyrazole having one hydrogen substituted by one R^3 group, claim 10 embraces crizotinib and reads on the approved product.

Claim 11 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 4



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or a pharmaceutically acceptable salt or hydrate thereof, in which

R^1 is selected from C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, $-S(O)_mR^4$, $-SO_2NR^4R^5$, $-S(O)_2OR^4$, $-NO_2$, $-NR^4R^5$, $-(CR^6R^7)_nOR^4$, -CN, $-C(O)R^4$, $-OC(O)R^4$, $-O(CR^6R^7)_nR^4$, $-NR^4C(O)R^5$, $-(CR^6R^7)_nC(O)OR^4$, $-(CR^6R^7)_nNCR^4R^5$, $-C(=NR^6)NR^4R^5$, $-NR^4C(O)NR^5R^6$, $-NR^4S(O)_pR^5$ or $-C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl or 3-12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5-12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic or 5-12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -CN, -O-C_{1-12} alkyl, -O-$(CH_2)_nC_{3-12}$ cycloalkyl, -O-$(CH_2)_nC_{6-12}$ aryl, -O-$(CH_2)_n$(3-12 membered heteroalicyclic) or -O-$(CH_2)_n$(5-12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, $-S(O)_mR^4$, $-SO_2NR^4R^5$, $-S(O)_2OR^4$, $-NO_2$, $-NR^4R^5$, $-(CR^6R^7)_nOR^4$, -CN, $-C(O)R^4$, $-OC(O)R^4$, $-NR^4C(O)R^5$, $-(CR^6R^7)_nC(O)OR^4$, $-(CR^6R^7)_nNCR^4R^5$, $-NR^4C(O)NR^5R^6$, $-NR^4S(O)_pR^5$ or $-C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3-12 membered heteroalicyclic, C_{6-12} aryl or 5-12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5-12 membered heteroaryl, C_{3-12} cycloalkyl or 3-12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3-12 membered heteroalicyclic, 5-12 membered heteroaryl, -O-C_{1-12} alkyl, -O-$(CH_2)_nC_{3-12}$ cycloalkyl, -O-$(CH_2)_nC_{6-12}$ aryl, -O-$(CH_2)_n$(3-12 membered heteroalicyclic), -O-$(CH_2)_n$(5-12 membered heteroaryl) or -CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, -OH, -CN, -C_{1-12} alkyl which may be partially or fully halogenated, -O-C_{1-12} alkyl which may be partially or fully halogenated, -CO, -SO and $-SO_2$;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

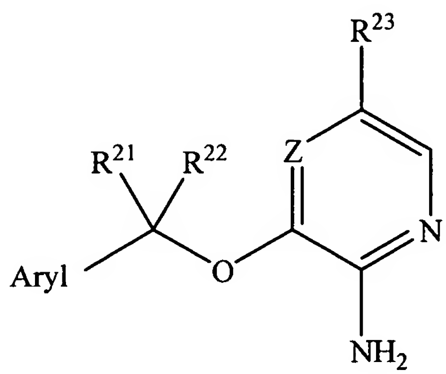
p is 1 or 2;

wherein said 3-12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5-12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine.

When R^1 is a 5-12 membered heteroaryl substituted by one R^3 group (where 5-12 membered heteroaryl is pyrazole, R^3 is 3-12 membered heteroalicyclic, and 3-12 membered heteroalicyclic is piperidine), one of R^9 or R^{10} is C_{1-12} alkyl, the other of R^9 or R^{10} is hydrogen, A^2 is C_{6-12} aryl substituted by three R^3 groups that are each halogen, the compound of the formula 4 embraces crizotinib. Therefore, claim 11 reads on the approved product.

Claim 12 of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 4 in which the definition of R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, m, n and p are the same as in claim 11, but the definition of A^2 is restricted. In the restricted definition, A^2 can be C_{6-12} aryl or 5-12 membered heteroaryl optionally substituted by one or more R^3 groups. Thus when A^2 is C_{6-12} aryl, claim 12 embraces crizotinib and reads on the approved product.

Claim 13 of U.S. Patent No. 7,230,098, (as corrected by the Certificate of Correction filed on September 8, 2011, a copy of which is attached hereto, claims the genus of chemical compounds of formula 6



6

or a pharmaceutically acceptable salt thereof in which

Z is CH or N;

Aryl is an optionally fused aryl or an optionally fused heteroaryl group which is optionally substituted by one or more substituents selected from the group consisting of a

halogen, $-OR^{24}$, $-COR^{24}$, $-COOR^{24}$, $-CONR^{24}R^{25}$, -CN, $-NO_2$, $-S(O)_mR^{24}$, $-SO_2NR^{24}R^{25}$, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, aryl, $-NR^{24}R^{25}$, $-NR^{24}C(O)R^{25}$ and $-NR^{24}S(O)_pR^{25}$;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, halogen, $-COR^{24}$, $-COOR^{24}$, $-CONR^{24}R^{25}$, -CN, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, and aryl;

R^{23} is selected from the group consisting of:

an optionally fused aryl, heteroaryl, alicyclic or heterocyclic group, optionally substituted by one or more substituents selected from the group consisting of a halogen, $-(CH_2)_n-OR^{24}$, $-COR^{24}$, $-COOR^{24}$, $-CONR^{24}R^{25}$, -CN, $-NO_2$, $-S(O)_mR^{24}$, $-SO_2NR^{24}R^{25}$, perfluoroalkyl, -O-perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, heteroaryl, alkenyl, alkynyl, aryl, $-(CH_2)_n-NR^{24}R^{25}$, $-NR^{24}C(O)R^{25}$ and $-NR^{24}S(O)_pR^{25}$, wherein said heterocycle, heteroaryl and aryl substituents may be optionally substituted by a group selected from the group consisting of lower alkyl, halogen, $-C(O)NR^{24}R^{25}$, $NR^{24}R^{25}$, $NR^{24}C(O)R^{25}$ and $NR^{24}S(O)_pR^{25}$;

$-OR^{24}$, $-COR^{24}$, $-COOR^{24}$, -CN, $-NO_2$, $-S(O)_mR^{24}$, $-SO_2NR^{24}R^{25}$, perfluoroalkyl, cycloalkyl, heterocycle, alkenyl, and alkynyl;

R^{24} and R^{25} are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aminoalkyl, alkylaminoalkyl, alkylaminocycloalkyl, dialkylaminoalkyl and $-(CH_2)_n$-heterocycle, wherein said $-(CH_2)_n$-heterocycle may be further substituted by one or more of lower alkyl, $-(CH_2)_n$-hydroxy, heterocycle and $-C(O)R^{26}$,

or R^{24} and R^{25} can combine to form a 5- to 6-membered heterocyclic ring having one or more heteroatoms selected from the group consisting of N, O, S, S(O) and SO_2, said 5- to 6-membered heterocyclic ring may be optionally substituted by lower alkyl, $-(CH_2)_n$-heterocycle, cycloalkyl, halo, $-(CH_2)_n-NR^{26}R^{27}$, amino, $-C(O)R^{26}$, $-NR^{26}-C(O)OR^{27}$ and $-NR^{26}-C(O)R^{27}$;

wherein R^{26} and R^{27} are independently selected from the group consisting of hydrogen, lower alkyl, $-(CH_2)_n$-cycloalkyl and $-C(O)-(CH_2)_n-OH$;

except that when Z is N and R^{21} and R^{22} are H and Aryl is m-chlorophenyl, R^{23} is not piperazine;

m is 0, 1 or 2;

n is 0, 1, 2 or 3;

p is 1 or 2;

wherein said heterocyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine.

When Z is CH, Aryl is substituted by three halogen groups, one of either R^{21} or R^{22} is hydrogen, the other of R^{21} or R^{22} is lower alkyl, R^{23} is heteroaryl group substituted by heterocycle, where the heteroaryl group is pyrazole. Thus, the compound of formula 6 embraces crizotinib. Therefore, claim 13 reads on the approved product.

<u>Claim 14</u> of U.S. Patent No. 7,230,098 claims the genus of chemical compounds of formula 6 in which the definition of Z, Aryl, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, m, n and p are the same as in claim 13, but the definition of R^{23} is restricted. In the restricted definition, R^{23} can be aryl or heteroaryl. Thus, when R^{23} is heteroaryl, claim 14 embraces crizotinib and reads on the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) IND 73,544 was assigned to crizotinib in a letter dated December 22, 2005. Accordingly, the effective date of IND 73,544 is January 21, 2006, *i.e.,* thirty-days following the notification of December 22, 2005.

(b) An NDA under §505(b) of the Federal Food, Drug and Cosmetic Act for Xalkori™ (crizotinib) was submitted on March 30, 2011 as NDA 202570. The NDA for Xalkori™ was submitted under the fast track program. The first wave submission for NDA 202570 was completed under the fast track program on January 4, 2011. The second and third wave submissions for NDA 202570 were completed on February 22, 2011 and March 30, 2011, respectively. Subsequent filings were made on March 31, 2011, April 13, 2011, April 15, 2011, April 26, 2011 and May 3, 2011. NDA 202570 was determined to be complete and ready for substantive review in a letter from FDA on May 16, 2011. FDA accorded NDA 202570 a submission date of March 30, 2011, a copy of which is attached hereto as EXHIBIT D.

(c) NDA No. 202570 was approved on August 26, 2011.

(11) A brief description of the significant activities undertaken by, or for, the marketing Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, is attached hereto as EXHIBIT E.

(12) Pursuant to the provisions of 35 U.S.C. §156, Applicant believes U.S. Patent No. 7,230,098 is eligible for an extension of 178 days. The requirements of 35 U.S.C. §156(a) and (c)(4) have been satisfied as follows:

(a) U.S. Patent No. 7,230,098 claims the approved product, Xalkori™ (crizotinib).

(b) U.S. Patent No. 7,230,098 has not yet expired. It is presently set to expire on March 1, 2025. The expiration date of U.S. Patent No. 7,230,098 includes 369 days of patent term adjustment granted under 35 U.S.C 154(b).

(c) The term of U.S. Patent No. 7,230,098 has never been extended.

(d) This Application is being submitted by PFIZER, the owner of record of U. S. Patent No. 7,230,098, in accordance with the requirements of 35 U.S.C. §156(d).

(e) The approved product, Xalkori™, has been subject to a regulatory review period under §505(b) of the Federal Food, Drug and Cosmetic Act prior to its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(f) No patent has, to this date, been extended, nor has any other extension been applied for, for the regulatory review period forming the basis for this Application for extension of the term of U.S. Patent No. 7,230,098.

The length of extension of the term of U.S. Patent No. 7,230,098 of 178 days claimed by applicant was determined according to the provisions of 35 U.S.C. §156(c) and §156(g) as follows:

(a) The term of the regulatory review period, as defined in 35 U.S.C. §156(c)(2), is 693.5 days, *i.e.,* one half of the 1387 day period between the June 12, 2007 issue date of U.S. Patent No. 7,230,098 and the March 30, 2011 submission date of the NDA.

(b) The term of the NDA review period commencing on March 30, 2011, the date the NDA for the approved product was initially submitted, and ending August 26, 2011, the date on which the NDA was approved, is 150 days.

(c) The sum of paragraphs (a) and (b) of this subsection is 843 days ignoring the extra half day.

(d) The sum shown in paragraph (c) is limited under 35 U.S.C. 156(c)(3) because fourteen years from the NDA approval date of August 26, 2011 is earlier than the June 23, 2027 expiration of U.S. Patent No. 7,230,098 based on a 843 day extension of patent term.

(e) The date that is fourteen years from the NDA approval date is August 26, 2025.

(f) The sum total of days between the expiration of U.S. Patent No. 7,230,098 of March 1, 2025 and the date August 26, 2025 which is the date fourteen years from the NDA approval date is 178 days.

(g) The sum shown in paragraph (f) is not limited under 35 U.S.C. 156 (g)(6)(A) which states that if the patent involved is issued after the date of enactment of that section, the period of extension may not exceed five (5) years. The claimed period of extension is 178 days, which period is less than five (5) years.

(h) The sum in paragraph (f) is 178 days.

(i) Pursuant to 35 U.S.C. §156, Applicant herewith claims an extended expiration date of August 26, 2025, for U.S. Patent No. 7,230,098.

(13) Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information material to the determination of entitlement to the 178 day extension being sought to the term of U.S. Patent No. 7,230,098.

(14) The prescribed fee pursuant to 37 C.F.R. §1.20(j)(1) of $1,120.00 for receiving and acting upon this Application for extension of patent term is to be charged to Deposit Account No. 16-1445, as authorized in the transmittal letter.

(15) Please address all inquiries and correspondence relating to this Application to:

Vincent P. Liptak
PFIZER INC.
Patent Department
10555 Science Center Dr.
San Diego, CA 92121

Tel.: (858) 622-7908

(16) Pursuant to 37 C.F.R. §1.740(15)(b) and M.P.E.P. §2753, one (1) original Application for Patent Term Extension of U.S. Patent No. 7,230,098, with accompanying exhibits, and two (2) copies of such papers and exhibits, are submitted herewith.

Respectfully submitted,

Vincent P. Liptak
Attorney for Applicants
Reg. No. 53,225

Date: September 14, 2011
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EXHIBIT A

COPY OF
US PATENT NO. 7,230,098

624 PAGES

US007230098B2

(12) **United States Patent**
Cui et al.

(10) **Patent No.:** **US 7,230,098 B2**
(45) **Date of Patent:** **Jun. 12, 2007**

(54) **AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 369 days.

(21) Appl. No.: **10/786,610**

(22) Filed: **Feb. 26, 2004**

(65) **Prior Publication Data**

US 2005/0009840 A1 Jan. 13, 2005

Related U.S. Application Data

(60) Provisional application No. 60/540,229, filed on Jan. 29, 2004, provisional application No. 60/449,588, filed on Feb. 26, 2003.

(51) **Int. Cl.**

C07D 417/00	(2006.01)
C07D 413/00	(2006.01)
C07D 401/00	(2006.01)
C07D 211/68	(2006.01)
C07D 211/72	(2006.01)

(52) **U.S. Cl.** 544/60; 544/124; 544/215; 544/238; 544/333; 544/360; 544/405; 546/194; 546/297

(58) **Field of Classification Search** .... None
See application file for complete search history.

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Primary Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Foley & Lardner LLP

(57) **ABSTRACT**

Aminopyridine and aminopyrazine compounds of formula (1), compositions including these compounds, and methods of their use are provided. Preferred compounds of formula 1 have activity as protein kinase inhibitors, including as inhibitors of c-MET

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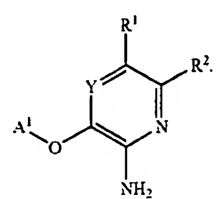

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AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

This application claims the benefit of U.S. Provisional Application Ser. No. 60/449,588, filed Feb. 26, 2003, and 60/540,229, filed Jan. 29, 2004, the disclosures of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The invention relates generally to novel chemical compounds and methods. More particularly, the invention provides novel aminoheteroaryl compounds, particularly aminopyridines and aminopyrazines, having protein tyrosine kinase activity, and methods of their synthesis and use.

BACKGROUND

Protein kinases ("PKs") are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine résidues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation, i.e., virtually all aspects of cell life in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

The PKs can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

One of the prime aspects of PTK activity is their involvement with growth factor receptors. Growth factor receptors are cell-surface proteins. When bound by a growth factor ligand, growth factor receptors are converted to an active form which interacts with proteins on the inner surface of a cell membrane. This leads to phosphorylation on tyrosine residues of the receptor and other proteins and to the formation inside the cell of complexes with a variety of cytoplasmic signaling molecules that, in turn, effect numerous cellular responses such as cell division (proliferation), cell differentiation, cell growth, expression of metabolic effects to the extracellular microenvironment, etc. For a more complete discussion, see Schlessinger and Ullrich, *Neuron* 9:303–391 (1992), which is incorporated by reference, including any drawings, as if fully set forth herein.

Growth factor receptors with PTK activity are known as receptor tyrosine kinases ("RTKs"). They comprise a large family of transmembrane receptors with diverse biological activity. At present, at least nineteen (19) distinct subfamilies of RTKs have been identified. An example of these is the subfamily designated the "HER" RTKs, which include EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. These RTKs consist of an extracellular glycosylated ligand binding domain, a transmembrane domain and an intracellular cytoplasmic catalytic domain that can phosphorylate tyrosine residues on proteins.

Another RTK subfamily consists of insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to form a heterotetramer of two entirely extracellular glycosylated α subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain.

A third RTK subfamily is referred to as the platelet derived growth factor receptor ("PDGFR") group, which includes PDGFRα, PDGFRβ, CSFIR, c-kit and c-fms. These receptors consist of glycosylated extracellular domains composed of variable numbers of immunoglobin-like loops and an intracellular domain wherein the tyrosine kinase domain is interrupted by unrelated amino acid sequences.

Another group which, because of its similarity to the PDGFR subfamily, is sometimes subsumed into the later group is the fetus liver kinase ("flk") receptor subfamily. This group is believed to be made up of kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1).

A further member of the tyrosine kinase growth factor receptor family is the fibroblast growth factor ("FGF") receptor subgroup. This group consists of four receptors, FGFR1–4, and seven ligands, FGF1–7. While not yet well defined, it appears that the receptors consist of a glycosylated extracellular domain containing a variable number of immunoglobin-like loops and an intracellular domain in which the tyrosine kinase sequence is interrupted by regions of unrelated amino acid sequences.

Still another member of the tyrosine kinase growth factor receptor family is the vascular endothelial growth factor ("VEGF") receptor subgroup. VEGF is a dimeric glycoprotein similar to PDGF but has different biological functions and target cell specificity in vivo. In particular, VEGF is presently thought to play an essential role is vasculogenesis and angiogenesis.

Still another member of the tyrosine kinase growth factor receptor family is MET, often referred to as c-Met, also known as human hepatocyte growth factor receptor tyrosine kinase (hHGFR). c-Met is thought to play a role in primary tumor growth and metastasis.

A more complete listing of the known RTK subfamilies is described in Plowman et al., DN&P, 7(6):334–339 (1994), which is incorporated by reference.

In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases." This latter designation, abbreviated "CTK," will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appear so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, AUR1, AUR2 and Yrk. For a more detailed discussion of CTKs, see Bolen, *Oncogene*, 8:2025–2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

The serine/threonine kinases, STKs, like the CTKs, are predominantly intracellular although there are a few receptor kinases of the STK type. STKs are the most common of the cytosolic kinases; i.e., kinases that perform their function in that part of the cytoplasm other than the cytoplasmic organelles and cytoskelton. The cytosol is the region within the cell where much of the cell's intermediary metabolic and biosynthetic activity occurs; e.g., it is in the cytosol that proteins are synthesized on ribosomes. The STKs include CDk2, Raf, the ZC family of kinases, the NEK family of kinases, and BUB1.

RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including, significantly, cancer. Other pathogenic conditions which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders,

immunological disorders such as autoimmune disease, cardiovascular disease such as atherosclerosis and a variety of renal disorders.

With regard to cancer, two of the major hypotheses advanced to explain the excessive cellular proliferation that drives tumor development relate to functions known to be PK regulated. That is, it has been suggested that malignant cell growth results from a breakdown in the mechanisms that control cell division and/or differentiation. It has been shown that the protein products of a number of proto-oncogenes are involved in the signal transduction pathways that regulate cell growth and differentiation. These protein products of proto-oncogenes include the extracellular growth factors, transmembrane growth factor PTK receptors (RTKs), cytoplasmic PTKs (CTKs) and cytosolic STKs, discussed above.

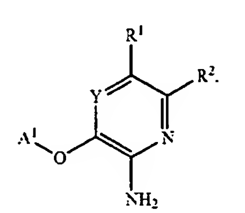
In view of the apparent link between PK-related cellular activities and wide variety of human disorders, it is no surprise that a great deal of effort is being expended in an attempt to identify ways to modulate PK activity. Some of these have involved biomimetic approaches using large molecules patterned on those involved in the actual cellular processes (e.g., mutant ligands (U.S. Pat. No. 4,966,849); soluble receptors and antibodies (Application No. WO 94/10202, Kendall and Thomas, *Proc. Nat'l Acad. Sci.*, 90:10705–10709 (1994), Kim, et al., *Nature*, 362:841–844 (1993)); RNA ligands (Jelinek, et al., *Biochemistry*, 33:10450–56); Takano, et al., *Mol. Bio. Cell*, 4:358A (1993); Kinsella, et al., *Exp. Cell Res.*, 199:56–62 (1992); Wright, et al., *J. Cellular Phys.*, 152:448–57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Pat. No. 5,330,992; Mariani, et al., *Proc. Am. Assoc. Cancer Res.*, 35:2268 (1994)).

In addition to the above, attempts have been made to identify small molecules which act as PK inhibitors. For example, bis-monocylic, bicyclic and heterocyclic aryl compounds (PCT WO 92/20642), vinylene-azaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridylquinolones (U.S. Pat. No. 5,330,992) have been described as tyrosine kinase inhibitors. Styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), quinazoline derivatives (EP Application No. 0 566 266 A1), selenaindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have all been described as PTK inhibitors useful in the treatment of cancer.

SUMMARY

In one embodiment, the invention provides a compound of formula 1

1



wherein:

Y is N or CR^{12};

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^6R^7)_nR^4$, —$C(O)_nR^4$, —$C(O)OR^4$, —CN, —NO_2, —$S(O)_mR^4$, —SO_2NR^4R, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR)NR^4R^5$, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, and each hydrogen in R^2 is optionally substituted by one or more R^8 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is —$(CR^9R^{10})_n$-A^2 except that:

(i) when Y is N and R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, A^1 is —$(CR^9R^{10})_n$-A^2 and n is not zero; and

(ii) when Y is N and R^2 is H and A^1 is m-chlorobenzyl, R^1 is not unsubstituted piperazine;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-2} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, $S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-2} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

R^{12} is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^4$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, and each hydrogen in R^{12} is optionally substituted by one or more R^3 groups;

R^1 and R^2 or R^1 and R^{12} may be combined together to form a C_{1-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

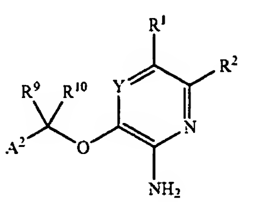
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a particular aspect of this embodiment, Y is N. In a preferred aspect, R^1 is not piperazine. In another preferred aspect, R^1 is not heteroalicyclic.

In another particular aspect of this embodiment, Y is CR^{12}.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, the compound has formula 1a

1a



wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^1 is selected from C_{1-12} aryl and 5–12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is selected from C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^6R^7)_nR^4$, —$C(O)R^4$, —$C(O)OR^4$, —CN, —NO_2, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR)NR^4R^5$, C_{1-9} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, A^2 is substituted by at least one halogen atom.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^2 is hydrogen, R^9 and R^{10} are independently C_{1-4} alkyl, and A^2 is phenyl substituted by at least one halogen atom.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

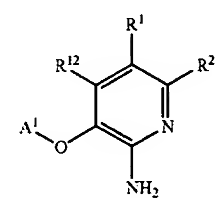
In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. In a more particular aspect, R^1 is not heteroalicyclic.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a fused ring heteroaryl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a —$SO_2NR^4R^5$ group.

In another embodiment, the invention provides a compound of formula 2

2



wherein:

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^6R^7)_nR^4$, —$C(O)R^4$, —$C(O)OR^4$, —CN, —NO_2, $S(O)_mR^4$, —$SO_2NR^4R^5$, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR)NR^4R^5$, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$,

—$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^1$ or —$C(O)NR^4R^5$, and each hydrogen in R^2 is optionally substituted by one or more R^8 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)OR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{1-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R_6 and R_7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is —$(CR^9R^{10})_n$-A^2;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$NR^4C(O)R^4$, —$(CR^6R^7)_nC(O)OR$, —$(CR^6R^7)_nNCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{1-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{1-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

R^{12} is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5—$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, and each hydrogen in R^{12} is optionally substituted by one or more R^3 groups;

R^1 and R^2 or R^1 and R^{12} may be combined together to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

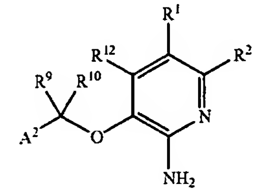
m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a particular aspect of this embodiment, the compound has formula 2a



2a

wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^1 is selected from C_{6-12} aryl and 5–12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is selected from C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^6R^7)_nR^4$, —$C(O)R^4$, —$C(O)OR^4$, —CN, —NO_2, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR)NR^4R^5$, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, A^2 is substituted by at least one halogen atom.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^2 is hydrogen, R^9 and R^{10} are independently C_{1-4} alkyl, and A^2 is phenyl substituted by at least one halogen atom.

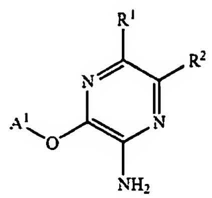
In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a fused ring heteroaryl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a —$SO_2NR^4R^5$ group.

In another embodiment, the invention provides a compound of formula 3

3



wherein:

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^5R^7)_nR^4$, —$C(O)R^4$, —$C(O)OR^4$, —CN, —NO_2, $S(O)_mR^4$, —$SO_2NR^4R^5$, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR^6)NR^4R^5$, C_{1-4} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, and each hydrogen in R^2 is optionally substituted by one or more R^8 groups;

R^3 is halogen, C_{1-2} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^5)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is —$(CR^9R^{10})_n$-A^2 except that:

(i) when R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, A^1 is —$(CR^9R^{10})_n$-A^2 and n is not zero; and

(ii) when R^2 is H and A^1 is m-chlorobenzyl, R^1 is not unsubstituted piperazine;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

R^1 and R^2 may be combined together to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

m is 0, 1 or 2;

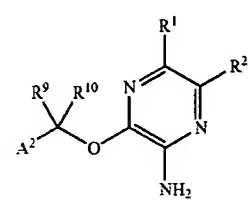
n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a particular aspect of this embodiment, the compound has formula 3a

3a



wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^1 is selected from C_{6-12} aryl and 5–12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is

selected from C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —O(CR^{6}R^7)$_n$R^4, —C(O)R^4, —C(O)OR^4, —CN, —NO$_2$, —S(O)$_m$R^4, —SO$_2$NR^{4}R^5, —C(O)NR^{4}R^5, —NR^{4}C(O)R^5, —C(=NR)NR^{4}R^5, C_{1-4} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, A^2 is substituted by at least one halogen atom.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment, R^2 is hydrogen, R^9 and R^{10} are independently C_{1-4} alkyl, and A^2 is phenyl substituted by at least one halogen atom.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

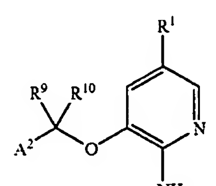
In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups. In still more particular aspects, R^1 is not heteroalicyclic.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a fused ring heteroaryl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

In particular aspects of this embodiment, and in combination with any other particular aspects of this embodiment not inconsistent with the following definition of R^1, R^1 is a —SO$_2$NR^{4}R^5 group.

In another embodiment, the invention provides a compound of formula 4

4



wherein:

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —O(CR^{6}R^7)$_n$R^4, —C(O)R^4, —C(O)OR^4, —CN, —NO$_2$, —S(O)$_m$R^4, —SO$_2$NR^{4}R^5, —C(O)NR^{4}R^5, —NR^{4}C(O)R^5, —C(=NR^6)NR^{4}R^5, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —S(O)$_m$R^4, —SO$_2$NR^{4}R^5, —S(O)$_2$OR^4, —NO$_2$, —NR^{4}R^5, —(CR^{6}R^7)$_n$OR^4, —CN, —C(O)R^4, —OC(O)R^4, —O(CR^{6}R^7)$_n$R^4, —NR^{4}C(O)R^5, —(CR^{6}R^7)$_n$C(O)OR^4, —(CR^{6}R^7)$_n$NCR^{4}R^5, —C(=NR^6)NR^{4}R^5, —NR^{4}C(O)NR^{5}R^6, —NR^{4}S(O)$_p$R^5 or —C(O)NR^{4}R^5, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—(CH$_2$)$_n$$C_{3-12}$ cycloalkyl, —O—(CH$_2$)$_n$$C_{6-12}$ aryl, —O—(CH$_2$)$_n$(3–12 membered heteroalicyclic) or —O—(CH$_2$)$_n$(5–12 membered heteroaryl); and each hydrogen in R^9 is optionally substituted by one or more R^{11} groups;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —S(O)$_m$R^4, —SO$_2$NR^{4}R^5, —S(O)$_2$OR^4, —NO$_2$, —NR^{4}R^5, —(CR^{6}R^7)$_n$OR^4, —CN, —C(O)R^4, —OC(O)R^4, —NR^{4}C(O)R^5, —(CR^{6}R^7)$_n$C(O)OR^4, —(CR^{6}R^7)$_n$NCR^{4}R^5, —NR^{4}C(O)NR^{5}R^6, —NR^{4}S(O)$_p$R^5 or —C(O)NR^{4}R^5; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—(CH$_2$)$_n$$C_{3-12}$ cycloalkyl, —O—(CH$_2$)$_n$$C_{6-12}$ aryl, —O—(CH$_2$)$_n$(3–12 membered heteroalicyclic), —O—(CH$_2$)$_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO$_2$;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

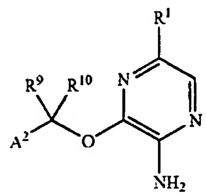
p is 1 or 2;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a particular aspect of this embodiment, A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

In other particular aspects of this embodiment, preferred substituents and groups of substituents include those defined in particular aspects of the previous embodiments.

In another embodiment, the invention provides a compound of formula 5



wherein:

R^1 is selected from C_{1-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, —$O(CR^6R^7)_nR^4$, —$C(O)R^4$, —$C(O)OR^4$, —CN, —NO_2, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$C(O)NR^4R^5$, —$NR^4C(O)R^5$, —$C(=NR^6)NR^4R^5$, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{2-8} alkynyl; and each hydrogen in R^3 is optionally substituted by one or more R^3 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_rC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups; except that when R^2, R^9 and R^{10} are all H and A^2 is m-chlorophenyl, R^1 is not unsubstituted piperazine;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{1-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{1-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a particular aspect of this embodiment, A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

In other particular aspects of this embodiment, preferred substituents and groups of substituents include those defined in particular aspects of the previous embodiments.

In another embodiment, the invention provides a compound selected from the group consisting of: 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol; 3-(2,6-dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine; 3-[2-chloro-6-(1H-indol-4-yl)-benzyloxy]-5-(1H-indol-4-yl)-pyridin-2-ylamine; 2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-pyrrole-1-carboxylic acid tert-butyl ester; 3-(2,6-dichloro-benzyloxy)-5-(1H-pyrrol-2-yl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(4-fluoro-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(2-fluoro-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-fluoro-phenyl)-pyridin-2-ylamine; 5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine; N-4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide; N-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-acetamide; 3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol; 3-(2,6-dichloro-benzyloxy)-5-(4-methoxy-phenyl)-pyridin-2-ylamine; 5-(3-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol; 3-(2,6-dichloro-benzyloxy)-5-(2-phenoxy-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-isopropyl-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(2-methoxy-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine; N-{2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide; {4-[6-amino-5-

(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanol; 5-benzo[1,3]dioxol-5-yl-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(4-methyl-thiophen-2-yl)-pyridin-2-ylamine; 5-(2-benzyloxy-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-methoxy-phenyl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-2-yl)-pyridin-2-ylamine; 5-(4-benzyloxy-3-fluoro-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-diethylamino-ethyl)-benzamide; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-diethylamino-propyl)-benzamide; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl[(3S)-3-cyclopropylaminomethyl-piperidin-1-yl]-methanone; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide; (4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-(3-fluoro-piperidin-1-ylmethyl)-pyrrolidin-1-yl}-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-cyclopropyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-{(2R)-2-[(cyclopropylmethyl-amino)-methyl]-pyrrolidin-1-yl)methanone; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-cyclopropylmethyl-N-(2R)-pyrrolidin-2-ylmethyl-benzamide; 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-N-methyl-benzamide; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-{(2S)-2-[(3R)-3-hydroxy-pyrrolidin-1-ylmethyl]-pyrrolidin-1-yl)methanone; 3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid; {3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)-acetic acid; 2-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone; 2-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone; 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-yl)-pyridin-2-ylamine; (1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-carbamic acid tert-butyl ester; 3-(2,6-dichloro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyridin-2-ylamine; N-(1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-acetamide; 1-(4-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine; 1-(4-{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyridin-2-ylamine; N-(1-{5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-yl methyl-1H-indol-5-yl)-pyridin-2-ylamine; 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid ethyl ester; 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid; {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-(4-methyl-piperazin-1-yl)-methanone; (5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide; 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; (1-{5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carbonyl}-(3S)-pyrrolidin-3-yl)-carbamic acid tert-butyl ester; {5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}[(3S)-3-amino-pyrrolidin-1-yl]-methanone; 5-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-hydroxy-3-pyrrolidin-1-yl-propyl)-amide; 4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenol; 3-benzyloxy-5-phenyl-pyridin-2-ylamine; 3-(3-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-4-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2,5-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-5-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2,4-dichloro-5-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-3-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(3,4-dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 2-(2-amino-5-phenyl-pyridin-3-yloxymethyl)-benzonitrile; 3-(2-chloro-6-fluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine; 5-Phenyl-3-(2,3,6-trifluoro-benzyloxy)-pyridin-2-ylamine; 3-(2,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2,6-difluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(3-chloro-2,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(2-chloro-6-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine; 3-(3-Fluoro-4-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine; N-[3-(2-amino-5-phenyl-pyridin-3-yloxymethyl)-phenyl]-methanesulfonamide; 5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-3-(3-nitro-benzyloxy)-pyridin-2-ylamine; 5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-3-(naphthalen-1-ylmethoxy)-pyridin-2-ylamine;

3-(2-chloro-3,6-difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 2-[2-amino-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-3-yloxy)-N-(4-isopropyl-phenyl)-2-phenyl-acetamide; 3-(5-chloro-benzo[b]thiophen-3-ylmethoxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; (4-[6-amino-5-(4-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl) [(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; (4-[6-amino-5-(5-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-bromo-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl][(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenol; 3-(2,6-difluoro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine; 3-(2,6-difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl) [(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid ethyl ester; {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid; 2-{4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone; 2-{4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy)-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone; 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenol; 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenol; 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenol; 2-[2-amino-5-(4-hydroxy-phenyl)-pyridin-3-yloxymethyl]-benzonitrile; 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenol; 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenol; 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-y]-phenol; N-{4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-phenyl) methanesulfonamide; 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzamide; 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzoic acid; N-(4-{6-amino-5-[2-(4-methyl-piperazine-1-carbonyl)-benzyloxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-N-(2-hydroxy-ethyl)-benzamide; 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-N-isobutyl-benzamide; 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl)[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl)[(3S)-3-amino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl)piperazin-1-yl)-ethanone; 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl)(4-methyl-piperazin-1-yl)-methanone; 1-(4-{4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoyl)piperazin-1-yl)-ethanone; 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-benzoic acid; 2-{2-amino-5-[4-((2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{2-amino-5-[4-((2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{2-amino-5-[4-((3S)-3-dimethylamino-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{2-amino-5-[4-((3S)-3-amino-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{2-amino-5-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile; 2-{5-[4-(4-acetyl-piperazine-1-carbonyl)-phenyl]-2-amino-pyridin-3-yloxymethyl}-benzonitrile; 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl} [(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoyl)piperazin-1-yl)-ethanone; 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[6-amino-5-(2,4-dichloro-benzyloxy) pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2-trifluoromethyl-benzy-

loxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; [(3S)-3-amino-pyrrolidin-1-yl]-4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-methanone; {4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 1-(44-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone; 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(4-#tert!-butyl-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoyl) piperazin-1-yl)-ethanone; 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl)piperazin-1-yl)-ethanone; 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-y]-benzoic acid; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; (4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-amino-piperidin-1-yl)-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; (4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone; {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 3-[6-amino-5-(2chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)(4-amino-piperidin-1-yl)-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone; {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-amino-pyrrolidin-1-yl]-methanone; 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzamide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine; 5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-3-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-2-ylamine; 2-diethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-cyclopropylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-Pyrrolidin-1-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-morpholin-4-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)amide; 2-Piperidin-1-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-dimethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)amide; 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-

difluoro-benzyloxy)-pyridin-3-yl]-phenyl)-amide; 2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-[(2S)-2-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid (4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-Pyrrolidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-morpholin-4-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-diethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-dimethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-Piperidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-[(3R)-3-hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)amide; 2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 2-cyclopropylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(2-dimethylaminomethyl-phenyl)-pyridin-2-ylamine; compound with trifluoro-acetic acid; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-yl-phenyl)-pyridin-2-ylamine; compound with trifluoro-acetic acid; N-{4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl)methanesulfonamide; compound with trifluoro-acetic acid; 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid; {5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone; {5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (1-methyl-piperidin-4-yl)-amide; {5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(3,5-dimethyl-piperazin-1-yl)-methanone; 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide; {5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl)(3-dimethylamino-pyrrolidin-1-yl)-methanone; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-#N!-(2-morpholin-4-yl-ethyl)-benzamide; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzamide; 2-Piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-dimethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl)]-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-dimethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-[(3R)-3-hydroxy-pyrrolidin-1-yl)]-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another embodiment, the invention provides a compound selected from the group consisting of: 4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenol; 3-(2,6-dichloro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyrazin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; 3-(2,6-dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; 5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyrazin-2-ylamine; 4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-benzoic acid; {4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; {4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 2-morpholin-4-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-piperidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-pyrrolidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-

ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-dimethylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-diethylamino-ethanesulfonic acid {4-5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-cyclopropylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-[(3R)-3-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl)amide; 2-piperidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-diethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-morpholin-4-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-pyrrolidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-dimethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid (3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}amide; 2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid (3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 2-cyclopropylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone; {-4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2S)-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide; 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-propyl)-benzamide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyrazin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-yl)-pyrazin-2-ylamine; 1-(4-{5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl) piperazin-1-yl)-ethanone; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyrazin-2-ylamine; N-(1-{5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; compound with trifluoro-acetic acid; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; compound with trifluoro-acetic acid; N-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-methanesulfonamide; 2-pyrrolidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy}-pyrazin-2-yl}-phenyl)-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-piperidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-[(3R)-3-Hydroxy-pyrrolidin-1-y]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic

acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-morpholin-4-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-cyclopropylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3S)-3-amino-pyrrolidin-1-yl)-m-ethanone; (3-55 5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl)-m-ethanone; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl phenyl)-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; 3-{5-amino-6-[-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid; 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide; and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another embodiment, the invention provides a compound selected from the group consisting of: (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy)-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-amino-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-diethylamino-ethyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-y{)-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy)-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy}-pyridin-3-yl}-phenyl)-amide; 2-piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy)-pyridin-3-yl}-phenyl)-amide; 2-((R)-3-Hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy)-pyridin-3-yl}-phenyl)-amide; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl)benzoic acid; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy)-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-y!)phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,

6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl)-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl)pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-3-morpholin-4-yl-propan-2-ol; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diethylamino-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-3-ylmethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diisopropylamino-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-pyridin-2-ylamine; N-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl)-phenyl)-methanesulfonamide; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(1,1-dioxo-1lambda*6*-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine; N-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-phenyl-pyridin-2-ylamine; N-(4-{6-amino-5-[(R)-1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-thiophen-3-yl-pyridin-2-ylamine; 5-benzo[b]thiophen-2-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 4-methyl-piperazine-1-carboxylic acid (4-{1 -amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-phenyl)-amide; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea; 1-(4-(6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea; (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}phenyl)-amide; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea; (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea; 4-methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy}-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl}-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl)benzamide; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-

pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide; 4-methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide; 4-pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide; (3R,5S)-3,5-dimethyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(1-methyl-piperidin-4-yl)-urea; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(3-pyrrolidin-1-yl-propyl)-urea; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl)-urea; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(3-morpholin-4-yl-propyl)-urea; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-dimethylamino-prop-1-ynyl)-pyridin-2-ylamine; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)prop-2-ynyl)-urea; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-piperidin-1-yl-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-morpholin-4-yl-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-pyrrolidin-1-yl-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-((R)-3-hydroxy-pyrrolidin-1-yl)-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-(4-hydroxy-piperidin-1-yl)-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-dimethylamino-acetamide; N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)prop-2-ynyl)-2-diethylamino-acetamide; 2-(4-acetyl-piperazin-1-yl)-N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]pyridin-3-yl}-prop-2-ynyl)-acetamide; 4-methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide; (3R,5S)-3,5-dimethyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-1,1-dimethyl-prop-2-ynyl)-amide; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide; (S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl)-urea; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 4-pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-1,1-dimethyl-prop-2-ynyl)-amide; 3-(6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid cyclohexylamide; 3-(6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid isopropylamide; 4-(3-amino-3-methyl-but-1-ynyl)-2-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-phenylamine; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-y}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy)-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide; 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile; 6-amino-5-[1-(2,6-dichloro-3-cyano-phenyl)-ethoxy]-nicotinonitrile; 5-aminomethyl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid {6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl amide; N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-methanesulfonamide; N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-acetamide; N-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-4-methyl-benzenesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine; (S)-1-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-ethane-1,2-diol; (R)-1-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-ethane-1,2-diol; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrazol-4-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-diisopropylamino-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; 5-bromo-3-(3-fluoro-2-methoxy-benzyloxy)-pyridin-2-ylamine; 5-bromo-3-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-2-ylamine; {4-[6-amino-5-(3-fluoro-2-methoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 5-bromo-3-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-2-ylamine; {4-[6-amino-5-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 5-(4-amino-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid methyl ester; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyri-

din-3-yl}-phenoxy)-acetic acid; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-ethanone; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-3-hydroxy-pyrrolidin-1-yl}-ethanone; 4-[2-(4-{6-amino-5-[-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-phenoxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-ethanone; 5-bromo-3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-2-ylamine; {4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; N-{4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide; 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-(1H-pyrazol-4-yl)-pyridin-2-ylamine; 5-bromo-3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 5'-benzyloxy-[2,3]bipyridinyl-6'-ylamine; 5-benzyloxy-[3,3']bipyridinyl-6-ylamine; 3-benzyloxy-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-benzyloxy-[3,3']bipyridinyl-6,6'-diamine; 5'-(2-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 3-(2-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(4-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 3-(4-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(2-chloro-3,6-difluoro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,4']bipyridinyl-6-ylamine; 3-(2-chloro-3,6-difluoro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(2,6-dichloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,4']bipyridinyl-6-ylamine; 3-(2,6-dichloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3, 3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone; 5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine; 5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-pyrimidin-5-yl-pyridin-2-ylamine; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-6-ylamine; 5-benzyloxy-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-ethyl-butoxy)-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(3-methyl-butoxy)-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-butoxy-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-propoxy-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-cyclohexylmethoxy-pyridin-2-ylamine; 6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-ol; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-cyclohexyl-ethoxy)-pyridin-2-ylamine; 3-[-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-isobutoxy-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-phenethyloxy-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-2-ylmethoxy)-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-4-ylmethoxy)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 5-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-benzonitrile; 4-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperidin-4-ol; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperidin-1-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-pyrrolidin-1-yl-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-methyl-benzoic acid methyl ester; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(dimethyl-piperazin-1-ylmethyl)-phenyl]-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3,5-dimethoxy-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-methyl-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-[1,4]diazepan-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[1,4]diazepan-1-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperazin-1-yl-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-methanone; 5-[(1-benzyl-pyrrolidin-3-ylamino)-methyl]-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-

pyridin-2-ylamine; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-N-azetidin-3-yl-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-N,N-dimethyl-benzenesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1H-benzoimidazol-2-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1-methyl-1H-benzoimidazol-2-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(4-methyl-[1,4]diazepane-1-sulfonyl)-phenyl]-pyridin-2-ylamine; 6-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1-methyl-1H-indazole-3-carboxylic acid amide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-ylamine; 5-(3-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-3-methyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-fluoro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 5-benzo[1,3]dioxol-5-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)phenol; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dichloro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethyl-phenyl)-pyridin-2-ylamine; 5-(5-chloro-2-methoxy-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 5-(3-chloro-4-fluoro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(5-fluoro-2-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-isopropyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-ethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,4-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine; 5-(2-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 1-(2-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-fluoro-phenyl)-pyridin-2-ylamine; (2-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-o-tolyl-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethyl-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-morpholin-4-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-chloro-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)}-2-methyl-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-((2R,6S)-2,6-dimethyl-morpholin-4-ylmethyl)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-morpholin-4-ylmethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dimethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-m-tolyl-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dimethoxy-phenyl)-pyridin-2-ylamine; 5-biphenyl-3-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 5-(3,5-bis-trifluoromethyl-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-difluoro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dichloro-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-4-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-ethoxy-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; 7-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-2-phenyl-4H-pyrido[3,2-b][1,4]oxazin-3-one; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-ethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; 3-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester; 3-{2-amino-5-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester; {4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; [4-(6-amino-5-cyclohexylmethoxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(3-hydroxy-phenyl)-ethyl]-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(2,6-dichloro-phenyl)-ethyl]-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-(1-benzyl-piperidin-4-yl)-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone; {4[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-

methanone; (6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanone; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-morpholin-4-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-(2-pyrrolidin-1-yl-ethyl)-1H-[3,3']bipyridinyl-6-one; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-pyrrolidin-1-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-1H-[3,3']bipyridinyl-6-one; (4-{6-amino-5-[1-(2,4,6-trimethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-6-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-phenyl)-pyridin-2-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1H-[3,3']bipyridinyl-6-one; 5'-bromo-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-dimethylamino-phenyl)-pyridin-2-ylamine; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-2'-methoxy-[3,3']bipyridinyl-6-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-indol-5-yl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-thiazol-2-yl-pyridin-2-ylamine; (4-(6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-(1-methyl-1H-imidazol-2-yl)-pyridin-2-ylamine; {4-[6-amino-5-(2,4,6-trimethyl-benzyloxy)-pyridin-3-yl]-phenyl)(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-[6-amino-5-(2,3,5,6-tetramethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2,4,6-trifluoro-benzyloxy)-pyridin-3-yl]-phenyl) (4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-methyl-nicotinamidine; 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-(2-morpholin-4-yl-ethyl)-nicotinamidine; (4-{6-amino-5-[1-(2,4,5-trifluoro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(6-chloro-2-fluoro-3-methyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy)ethyl)-benzoic acid; and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another embodiment, the invention provides a compound selected from the group consisting of: 3-{5-amino-6-[-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl)-N-(1-methyl-piperidin-4-yl)-benzamide; 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide; {3-(5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-y phenyl)-(4-pyrrolidin-1-yl)-methanone; 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide;. {5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl)benzamide; 2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid; {3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-{2-[ethyl-(2-methoxy-ethyl)-amino]-ethyl}-benzamide; {3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; 3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzamide; {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone; {4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-

phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-ylphenyl}-(4-cyclopropylamino-piperidin-1-yl)-methanone; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((S)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 2-diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-((R)-3-Hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 2-pyrrolidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}phenyl)-amide; 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-cyclopropylamino-piperidin-1-yl)-methanone; 4{-5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((S)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide; 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide; 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-(5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-(5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-aminopyrrolidin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone hydrogen chloride; 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid; 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone hydrochloride salt; (3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 4-methyl-piperazine-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 1-(4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea; 4-methyl-piperazine-1-carboxylic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl)-phenyl)-amide; 1-(4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl) -phenyl)-3-(2-hydroxy-ethyl)-urea; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide; 1-(4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl-phenyl}-3-(1-methyl-piperidin-4-yl)-urea; 5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid; {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone; {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (5-[5-amino-6-(2-

chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 5-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; 3-[1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-{5-[(4-methylpiperazin-1-yl)carbonyl] pyridin-2-yl}-pyrazin-2-amine trifluoroacetate; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-pyridin-4-yl-pyrazin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrrol-2-yl}-pyrazin-2-ylamine; (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-methanone; (2-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-4-yl)-(4-methyl-piperazin-1-yl)-methanone; (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone; (5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-methanone; (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl)pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone; 6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide; 5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide; 6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide; 5-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide; (6-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-isopropyl-piperazin-1-yl)-methanone; and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 1 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 2 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 3 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 4 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 5 and pharmaceutically acceptable salts, hydrates and solvates thereof.

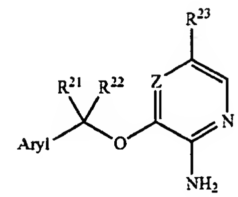
In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 6 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 7 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another aspect, the invention provides a compound selected from the group consisting of the compounds shown in Table 8 and pharmaceutically acceptable salts, hydrates and solvates thereof.

In another embodiment, the invention provides compounds having the following chemical structure (Formula 6):

(6)



wherein,

Z is CH or N;

Aryl is an optionally fused aryl or an optionally fused heteroaryl group which is optionally substituted by one or more substituents selected from the group consisting of a halogen, —OR^{24}, —COR^{24}, —$COOR^{24}$, —$CONR^{24}R^{25}$, —CN, —NO_2, —$S(O)_mR^{24}$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, aryl, —$NR^{24}R^{25}$, —$NR^{24}C(O)R^{25}$ and —$NR^{24}S(O)_pR^{25}$;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, halogen, —COR^{24}, —$COOR^{24}$, —$CONR^{24}R^{25}$, —CN, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, and aryl;

R^{23} is selected from the group consisting of:

an optionally fused aryl, heteroaryl, alicyclic or heterocyclic group, optionally substituted by one or more substituents selected from the group consisting of a halogen, —$(CH_2)_n$—OR^{24}, —COR^{24}, —$COOR^{24}$, —$CONR^{24}R$, —CN, —NO_2, —$S(O)_mR$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, —O-perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, heteroaryl, alkenyl, alkynyl, aryl, —(CH_2), —$NR^{24}R^{25}$, —$NR^{24}C(O)R^{25}$ and —$NR^{24}S(O)_pR^{25}$, wherein said heterocycle, heteroaryl and aryl substituents may be optionally substituted by a group selected from the group consisting of lower alkyl, halogen, —$C(O)NR^4R^2$, $NR^{24}R^2$, $NR^{24}C(O)R^{25}$ and $NR^{24}S(O)_pR^{25}$;

—OR^{24}, —COR^{24}, —$COOR^{24}$, —CN, —NO_2, —$S(O)_mR^{24}$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, cycloalkyl, heterocycle, alkenyl, and alkynyl;

R^{24} and R^{25} are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aminoalkyl, alkylaminoalkyl, alkylaminocycloalkyl, dialkylaminoalkyl and —$(CH_2)_n$-heterocycle, wherein said —$(CH_2)_n$-heterocycle may be further substituted by one or more of lower alkyl, —$(CH_2)_n$-hydroxy, heterocycle and —$C(O)R^{26}$,

or R^{24} and R^{25} can combine to form a 5- to 6-membered heterocyclic ring having one or more heteroatoms selected from the group consisting of N, O, S, S(O) and SO_2, said 5- to 6-membered heterocyclic ring may be optionally substituted by lower alkyl, —$(CH_2)_n$-heterocycle, cycloalkyl, halo, —$(CH_2)_n$—N R^2R^{27}, amino, —$C(O)R^{26}$, —NR^{26}—C(O)OR^27 and —NR^{26}—$C(O)R^{27}$;

wherein R^{26} and R^{27} are independently selected from the group consisting of hydrogen, lower alkyl, —$(CH_2)_n$-cycloalkyl and —C(O)—(CH_2), —OH;

except that when Z is N and R^{21} and R^{22} are H and Aryl is m-chlorophenyl, R^{23} is not piperazine;

m is 0, 1 or 2;

n is 0, 1, 2 or 3;

p is 1 or 2;

or a pharmaceutically acceptable salt thereof.

In preferred aspect of this embodiment, in the compound of Formula (6), R^{23} is aryl or heteroaryl.

In another preferred aspect of this embodiment, when Z is N, R^{23} is not heteroalicyclic.

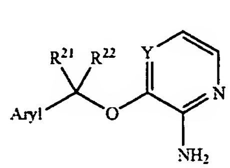
In another embodiment, the invention provides a pharmaceutical composition comprising any of the inventive compounds described herein. In particular aspects of this embodiment, the pharmaceutical composition comprises a compound of formula 1, a compound of formula 2, a compound of formula 3, a compound of formula 4, a compound of formula 5, a compound of formula 6, or a pharmaceutically acceptable salt, hydrate or solvate thereof, including particular aspects thereof as described above. In other particular aspects of this embodiment, the pharmaceutical composition comprises a compound selected from the compounds shown in Table 1, a compound selected from the compounds shown in Table 2, a compound selected from the compounds shown in Table 3, a compound selected from the compounds shown in Table 4, a compound selected from the compounds shown in Table 5, a compound selected from the compounds shown in Table 6, a compound selected from the compounds shown in Table 7, a compound selected from the compounds shown in Table 8, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Preferred compounds of the invention include those having c-MET inhibitory activity as defined by any one or more of IC_{50}, Ki, or percent inhibition. One skilled in the art can readily determine if a compound has such activity by carrying out the appropriate assay. In one embodiment, particularly preferred compounds have a c-MET IC_{50} of less than 5 μM, or less than 2 μM, or less than 1 μM, or less than 500 nM, or less than 400 nM, or less than 300 nM, or less than 200 nM, or less than 100 nM, or less than 50 nM. In another embodiment, particularly preferred compounds have a c-MET Ki of less than 5 μM or less than 2 μM, or less than 1 μM, or less than 500 nM, or less than 400 nM, or less than 300 nM, or less than 200 nM, or less than 100 nM, or less than 50 nM. In another embodiment, particularly preferred compounds have a c-MET inhibition at 1 μM of at least 10% or at least 20% or at least 30% or at least 40% or at least 50% or at least 60% or at least 70% or at least 80% or at least 90%.

In another embodiment, the invention provides a process of preparing the compound of Formula (6), comprising

(i) brominating a compound of the formula (a):

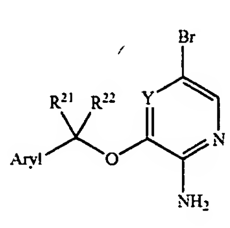
(a)



to give a compound of formula (b):

and

(b)



ii. reacting (b) with a boronic acid or ester derivative of the formula $R^{23}B(OR)_2$ in the presence of a palladium catalyst;

wherein R is hydrogen or an alcohol protecting group and Aryl, R^{21}, R^{22}, and R^{23} are as defined defined above.

In another embodiment, R^{23} is aryl or heteroaryl.

In another embodiment the invention provides a method of treating a subject suffering from a condition for which inhibition of Met receptor tyrosine kinase is indicated, comprising administering to the subject a therapeutically effective amount of any of the inventive compounds described herein.

The chemical formulae referred to herein may exhibit the phenomena of tautomerism and structural isomerism. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate RTK, CTK and/or STK activity and is not limited to any one tautomeric or structural isomeric form.

In addition, the formulae referred to herein may also exhibit stereoisomerism, in which such compounds may adopt an R or S configuration at chiral centers. Thus, this invention also encompasses any stereoisomeric form, their corresponding enantiomers (d- and l- or (+) and (−) isomers) and diastereomers thereof, and mixtures thereof, which possess the ability to modulate RTK, CTK and/or STK activity and is not limited to any one stereoisomeric form.

In particular embodiments, the compound is chosen from the compounds in Tables 1–8.

Another embodiment of the invention relates to a method of treating a subject suffering from a condition for which inhibition of protein kinase is indicated, comprising administering to the subject a therapeutically effective amount of any of the inventive compounds described herein.

Another aspect of this invention relates to a method for the modulation of the catalytic activity of a PK by contacting a PK with a compound of this invention or a physiologically acceptable salt thereof.

A further aspect of this invention is that the modulation of the catalytic activity of PKs using a compound of this invention may be carried out in vitro or in vivo.

A still further aspect of this invention is that the protein kinase whose catalytic activity is being modulated by a compound of this invention is selected from the group consisting of receptor protein tyrosine kinases, cellular tyrosine kinases and serine-threonine kinases.

It is an aspect of this invention that the receptor tyrosine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFRα, PDGFRβ, CSFIR, C-Kit, C-fms, Flk-1R, Flk-4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R, FGFR-4R, MET, DDR-1 and DDR-2.

In addition, it is an aspect of this invention that the cellular tyrosine kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

Another aspect of this invention is that the serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2, Raf, NEK and BUB1.

Another aspect of this invention relates to a method for treating or preventing a protein kinase related disorder in an organism comprising administering a therapeutically effective amount of any of the inventive compounds described herein to an organism, such as a mammal, particularly a human.

It is an aspect of this invention that the above-referenced protein kinase related disorder is selected from the group consisting of a receptor protein tyrosine kinase related disorder, a cellular tyrosine kinase disorder and a serine-threonine kinase related disorder.

In yet another aspect of this invention, the above referenced protein kinase related disorder is selected from the group consisting of a Met related disorder, an AUR^2 related disorder, a ZC1 related disorder, a PDGFR related disorder, an IGFR related disorder and a flk related disorder.

The above referenced protein kinase related disorders include by way of example and not limitation, cancers such as lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem glioma or pituitary adenomas), cancers of the blood such as acute myeloid leukemia, chronic mueloid leukemia, etc, Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides and benign prostatic hypertrophy, diabetes related diseases such as diabetic retinopathy, retinal ischemia and retinal neovascularization, hepatic cirrhosis, cardiovascular disease such as atherosclerosis, immunological disease such as autoimmune disease and renal disease. Preferably, the disease is cancer such as acute myeloid leukemia and colorectal cancer.

The above referenced protein kinase related disorder also includes disorders selected from the group consisting of diabetes, a hyper-proliferation disorder, hyperproliferative disorders of the kidney, von Hippel-Lindau disease, restenosis, fibrosis, psoriasis, osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis in yet another aspect of this invention.

Additional disorders which may be treated or prevented using the compounds of this invention are immunological disorders such as autoimmune diseases (e.g., AIDS, lupus, etc.) and cardiovascular disorders such as atherosclerosis.

It is an aspect of this invention that the protein kinase related disorder being treated or prevented by administration of a compound of this invention is a met kinase related disorder.

The organism in which the protein kinase related disorder is being treated or prevented is a human being in yet another aspect of this invention.

It is also an aspect of this invention that a compound described herein, or its salt, might be combined with other chemotherapeutic agents for the treatment of the diseases and disorders discussed above. For instance, a compound or salt of this invention might be combined with alkylating agents such as fluorouracil (5-FU) alone or in further combination with leukovorin; or other alkylating agents such as, without limitation, other pyrimidine analogs such as UFT, capecitabine, gemcitabine and cytarabine, the alkyl sulfonates, e.g., busulfan (used in the treatment of chronic granulocytic leukemia), improsulfan and piposulfan; aziridines, e.g., benzodepa, carboquone, meturedepa and uredepa; ethyleneimines and methylmelamines, e.g., altretamine, triethylenemelamine, triethylenephosphoramide, trethylenethiophosphoramide and trimethylolmelamine; and the nitrogen mustards, e.g., chlorambucil (used in the treatment of chronic lymphocytic leukemia, primary macroglobulinemia and non-Hodgkin's lymphoma), cyclophosphamide (used in the treatment of Hodgkin's disease, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, Wilm's tumor and rhabdomyosarcoma), estramustine, ifosfamide, novembrichin, prednimustine and uracil mustard (used in the treatment of primary thrombocytosis, non-Hodgkin's lymphoma, Hodgkin's disease and ovarian cancer); and triazines, e.g., dacarbazine (used in the treatment of soft tissue sarcoma).

Likewise a compound or salt of this invention might be expected to have a beneficial effect in combination with other antimetabolite chemotherapeutic agents such as, without limitation, folic acid analogs, e.g. methotrexate (used in the treatment of acute lymphocytic leukemia, choriocarcinoma, mycosis fungiodes breast cancer, head and neck cancer and osteogenic sarcoma) and pteropterin; and the purine analogs such as mercaptopurine and thioguanine which find use in the treatment of acute granulocytic, acute lymphocytic and chronic granulocytic leukemias.

A compound or salt of this invention might also be expected to prove efficacious in combination with natural product based chemotherapeutic agents such as, without limitation, the vinca alkaloids, e.g., vinblastin (used in the treatment of breast and testicular cancer), vincristine and vindesine; the epipodophylotoxins, e.g., etoposide and teniposide, both of which are useful in the treatment of testicular cancer and Kaposi's sarcoma; the antibiotic chemotherapeutic agents, e.g., daunorubicin, doxorubicin, epirubicin, mitomycin (used to treat stomach, cervix, colon, breast, bladder and pancreatic cancer), dactinomycin, temozolomide, plicamycin, bleomycin (used in the treatment of skin, esophagus and genitourinary tract cancer); and the enzymatic chemotherapeutic agents such as L-asparaginase.

In addition to the above, a compound or salt of this invention might be expected to have a beneficial effect used in combination with the platinum coordination complexes (cisplatin, etc.); substituted ureas such as hydroxyurea; methylhydrazine derivatives, e.g., procarbazine; adrenocortical suppressants, e.g., mitotane, aminoglutethimide; and hormone and hormone antagonists such as the adrenocorticosteriods (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate); estrogens (e.g., diethylstilbesterol); antiestrogens such as tamoxifen; androgens, e.g., testosterone propionate; and aromatase inhibitors (such as anastrozole.

Finally, the combination of a compound of this invention might be expected to be particularly effective in combination with mitoxantrone or paclitaxel for the treatment of solid tumor cancers or leukemias such as, without limitation, acute myelogenous (non-lymphocytic) leukemia.

The above method can be carried out in combination with a chemotherapeutic agent selected from the group consisting of mitotic inhibitors, alkylating agents, antimetabolites, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, antiangiogenic agents such as MMP-2, MMP-9 and COX-2 inhibitors, and anti-androgens.

Examples of useful COX-II inhibitors include VIOXX™, CELEBREX™ (alecoxib), valdecoxib, paracoxib, rofe-

coxib, and Cox 189. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain patent application number 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R,3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 3-[[(4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts and solvates of said compounds.

Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

A compound of the invention can also be used with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTINΘ (Genentech, Inc. of South San Francisco, Calif., USA). EGFR inhibitors are described in, for example in WO 95/19970 (published Jul. 27, 1995), WO 98/14451 (published Apr. 9, 1998), WO 98/02434 (published Jan. 22, 1998), and U.S. Pat. No. 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein.

EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, N.Y., USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, N.J., USA), and OLX-103 (Merck & Co. of Whitehouse Station, N.J., USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Mass.).

These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example 3-(2,4-Dimethylpyrrol-5-yl)methylene-2-indolinone, 5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, 3-[2,4-dimethyl-5-oxo-1,2-dihydroindole-3-ylidenemethyl)-1H-pyrrol-3-yl-propionic acid (Sugen Inc. of South San Francisco, Calif., USA), can also be combined with an inventive compound described herein. VEGF inhibitors are described in, for example in WO 99/24440, PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613, WO 99/61422 (published Dec. 2, 1999), U.S. Pat. No. 5,834,504 (issued Nov. 10, 1998), WO 01/60814, WO 02/04407, WO 98/50356, U.S. Pat. No. 5,883,113 (issued Mar. 16, 1999), U.S. Pat. No. 5,886,020 (issued Mar. 23, 1999), U.S. Pat. No. 5,792,783 (issued Aug. 11, 1998), WO 99/10349 (published Mar. 4, 1999), WO 97/32856 (published Sep. 12, 1997), WO 97/22596 (published Jun. 26, 1997), WO 98/54093 (published Dec. 3, 1998), WO 98/02438 (published Jan. 22, 1998), WO 99/16755 (published Apr. 8, 1999), and WO 98/02437 (published Jan. 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Wash., USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, Calif.; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colo.) and Chiron (Emeryville, Calif.). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Tex., USA) and 2B-1 (Chiron), can furthermore be combined with a compound any of the inventive compounds described herein, for example those indicated in WO 98/02434 (published Jan. 22, 1998), WO 99/35146 (published Jul. 15, 1999), WO 99/35132 (published Jul. 15, 1999), WO 98/02437 (published Jan. 22, 1998), WO 97/13760 (published Apr. 17, 1997), WO 95/19970 (published Jul. 27, 1995), U.S. Pat. No. 5,587,458 (issued Dec. 24, 1996), and U.S. Pat. No. 5,877,305 (issued Mar. 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in U.S. Provisional Application No. 60/117,341, filed Jan. 27, 1999, and in U.S. Provisional Application No. 60/117,346, filed Jan. 27, 1999, both of which are

incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the inventive compounds described herein.

The inventive compounds described herein can also be used with other agents useful in treating cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, of U.S. Pat. No. 6,258,824 B1. Specific CTLA4 antibodies that can be used in the present invention include those described in U.S. Provisional Application 60/113,647 (filed Dec. 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

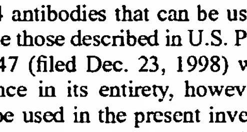
The above method can be also be carried out in combination with radiation therapy, wherein the amount of the inventive compound in combination with the radiation therapy is effective in treating the above diseases. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

Another aspect of the invention is directed to the use of any of the inventive compounds described herein in the preparation of a medicament, which is useful in the treatment of a disease mediated by abnormal Met kinase activity, such as cancer.

DETAILED DESCRIPTION

Definitions

The terms pyridine and pyrazine refer to the following structures respectively:



"Pharmaceutically acceptable salt" or "pharmaceutically acceptable salt thereof" refer to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, acetic acid, benzenesulfonic acid (besylate), benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, gluconic acid, glutamic acid, isethionic acid, lactic acid, maleic acid, malic acid, mandelic acid, mucic acid, pamoic acid, pantothenic acid, succinic acid, tartaric acid, and the like.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically acceptable salts thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

An "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives (including microcrystalline cellulose), gelatin, vegetable oils, polyethylene glycols, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or arrangements of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

The inventive compounds herein may exhibit the phenomena of tautomerism and structural isomerism. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate RTK, CTK and/or STK activity and is not limited to any one tautomeric or structural isomeric form.

It is contemplated that an inventive compound as described herein would be metabolized by enzymes in the body of the organism such as human being to generate a metabolite that can modulate the activity of the protein kinases. Such metabolites are within the scope of the present invention.

As used herein, "PK" refers to receptor protein tyrosine kinase (RTKs), non-receptor or "cellular" tyrosine kinase (CTKs) and serine-threonine kinases (STKs).

The term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of RTKs, CTKs and STKs. In particular, modulating refers to the

activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTK, CTK or STK is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

The term "catalytic activity" as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

The term "contacting" as used herein refers to bringing a compound of this invention and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly, i.e., by interacting with the kinase itself, or indirectly, i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished in vitro, i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PK related disorder, i.e., the IC_{50} of the compound, defined below, can be determined before use of the compounds in vivo with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the art, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

"In vitro" refers to procedures performed in an artificial environment such as, e.g., without limitation, in a test tube or culture medium. The skilled artisan will understand that, for example, an isolated PK may be contacted with a modulator in an in vitro environment. Alternatively, an isolated cell may be contacted with a modulator in an in vitro environment.

As used herein, "in vivo" refers to procedures performed within a living organism such as, without limitation, a mouse, rat, rabbit, ungulate, bovine, equine, porcine, canine, feline, primate, or human.

As used herein, "PK related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate, i.e., under or, more commonly, over, PK catalytic activity, where the particular PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs, (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth, or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of a PK refers to either amplification of the gene encoding a particular PK or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more of the symptoms of the cellular disorder increases). Under-activity is, of course, the converse, wherein the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases.

As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring an organism from acquiring a PK related disorder in the first place.

As used herein, the terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a PK mediated cellular disorder and/or its attendant symptoms. With regard particularly to cancer, these terms simply mean that the life expectancy of an individual affected with a cancer will be increased or that one or more of the symptoms of the disease will be reduced.

The term "organism" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukaryotic cell or as complex as a mammal. In a preferred aspect, the organism is a mammal. In a particularly preferred aspect, the mammal is a human being.

The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has the effect of (1) reducing the size of the tumor, (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis, (3) inhibiting to some extent (that is, slowing to some extent, preferably stopping) tumor growth, and/or, (4) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the cancer.

By "monitoring" is meant observing or detecting the effect of contacting a compound with a cell expressing a particular PK. The observed or detected effect can be a change in cell phenotype, in the catalytic activity of a PK or a change in the interaction of a PK with a natural binding partner. Techniques for observing or detecting such effects are well-known in the art. For example, the catalytic activity of a PK may be observed by determining the rate or amount of phosphorylation of a target molecule.

Reference to compounds of the invention includes pharmaceutically acceptable salts, solvates and hydrates thereof.

"Cell phenotype"refers to the outward appearance of a cell or tissue or the biological function of the cell or tissue. Examples, without limitation, of a cell phenotype are cell size, cell growth, cell proliferation, cell differentiation, cell survival, apoptosis, and nutrient uptake and use. Such phenotypic characteristics are measurable by techniques well-known in the art.

A "natural binding partner" refers to a polypeptide that binds to a particular PK in a cell. Natural binding partners can play a role in propagating a signal in a PK-mediated signal transduction process. A change in the interaction of the natural binding partner with the PK can manifest itself as an increased or decreased concentration of the PK/natural binding partner complex and, as a result, in an observable change in the ability of the PK to mediate signal transduction.

As used herein, "administer" or "administration" refers to the delivery of a compound or salt of the present invention or of a pharmaceutical composition containing a compound or salt of this invention to an organism for the purpose of prevention or treatment of a PK-related disorder.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as pharmaceutically acceptable excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

"Pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

"Pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the parent compound. Such salts include:

(1) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid; and

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

The inventive compounds described herein may also act as a prodrug. A "prodrug" refers to an agent, which is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug.

Indications

The PKs whose catalytic activity is modulated by the compounds of this invention include protein tyrosine kinases of which there are two types, receptor tyrosine kinases (RTKS) and cellular tyrosine kinases (CTKs), and serine-threonine kinases (STKs). RTK mediated signal transduction, is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects on the extracellular microenvironment, etc.). See, Schlessinger and Ullrich, *Neuron*, 9:303–391 (1992).

It has been shown that tyrosine phosphorylation sites on growth factor receptors function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Fantl et al., *Cell*, 69:413–423 (1992), Songyang et al., *Mol. Cell. Biol.*, 14:2777–2785 (1994), Songyang et al., *Cell*, 72:767–778 (1993), and Koch et al., *Science*, 252: 668–678 (1991). Several intracellular substrate proteins that associate with RTKs have been identified. They may be divided into two principal groups: (1) substrates that have a catalytic domain, and (2) substrates which lack such domain but which serve as adapters and associate with catalytically active molecules. Songyang et al., *Cell*, 72:767–778 (1993). The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., *Cell*, 72:767–778 (1993). These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

STKs, being primarily cytosolic, affect the internal biochemistry of the cell, often as a down-line response to a PTK event. STKs have been implicated in the signaling process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth and metabolism. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, glioblastoma and hemangioma, disorders such as leukemia, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy and other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

A precise understanding of the mechanism by which the compounds of the invention, in particular, the compounds generated in vivo from the compounds of the invention, inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of PKs. PKs typically possess a bi-lobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. More specifically, it is thought that the compounds of this invention binds in the general space normally occupied by the adenine ring of ATP.

In another aspect, the protein kinase, the catalytic activity of which is modulated by contact with a compound of this invention, is a protein tyrosine kinase, more particularly, a receptor protein tyrosine kinase. Among the receptor protein tyrosine kinases whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, selected from the group consisting of Met, Flk, FGFR, PDGFR, HER, IR, IGF, IRR, CSFIR, C-Kit, C-fms, flt. In a preferred aspect, the receptor protein tyrosine kinase whose catalytic activity can be modulated with a compound of this invention, or salt thereof.

The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, Aur2 and Yrk may be modulated by contact with a compound or salt of this invention.

Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2, Raf, NEK (including NEK 4a, NEK 4b, NEK 5 and NEK 6) and BUB1.

In another aspect, this invention relates to a method for treating or preventing a PK related disorder by administering a therapeutically effective amount of a compound of this invention, or a salt thereof, to an organism.

It is also an aspect of this invention that a pharmaceutical composition containing a compound of this invention, or a salt thereof, is administered to an organism for the purpose of preventing or treating a PK related disorder.

This invention is therefore directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby interfering with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including but not limited to carcinomas, sarcomas including Kaposi's sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma cancers such as lung cancer, NSCLC (non small cell ling cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lynphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem glioma or pituitary adenomas), cancers of the bloodsuch as acute myeloid leukemia, chronic mueloid leukemia, etc, Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides and benign prostatic hypertrophy, diabetes related diseases such as diabetic retinopathy, retinal ischemia and retinal neovascularization, hepatic cirrhosis, cardiovascular disease such as atherosclerosis, immunological disease such as autoimmune disease and renal disease. Preferably, the disease is cancer such as acute myeloid leukemia and colorectal cancer.

Further examples, without limitation, of the types of disorders related to inappropriate PK activity that the compounds described herein may be useful in preventing, treating and studying, are cell proliferative disorders, fibrotic disorders, metabolic disorders and infectious diseases.

Cell proliferative disorders, which may be prevented, treated or further studied by the present invention include cancer, blood vessel proliferative disorders and mesangial cell proliferative disorders.

Blood vessel proliferative disorders refer to disorders related to abnormal vasculogenesis (blood vessel formation) and angiogenesis (spreading of blood vessels). While vasculogenesis and angiogenesis play important roles in a variety of normal physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration, they also play a pivotal role in cancer development where they result in the formation of new capillaries needed to keep a tumor alive. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness.

Normal vasculogenesis and angiogenesis play important roles in a variety of physiological processes such as embryonic development, wound healing, organ regeneration and female reproductive processes such as follicle development in the corpus luteum during ovulation and placental growth after pregnancy. Folkman & Shing, *J. Biological Chem.*, 267(16):10931-10934 (1992). Uncontrolled vasculogenesis and/or angiogenesis has been associated with diseases such as diabetes as well as with malignant solid tumors that rely on vascularization for growth. Klagsbum & Soker, *Current Biology*, 3(10):699–702 (1993); Folkham, *J. Natl. Cancer Inst.*, 82:4–6 (1991); Weidner, et al., *New Engl. J. Med.*, 324:1-5 (1991).

As presently understood, the role of VEGF in endothelial cell proliferation and migration during angiogenesis and vasculogenesis indicates an important role for the KDR/FLK-1 receptor in these processes. Diseases such as diabetes mellitus (Folkman, 198, in XIth Congress of Thrombosis and Haemostasis (Verstraeta, et al., eds.), pp. 583–596, Leuven University Press, Leuven) and arthritis, as well as malignant tumor growth may result from uncontrolled angiogenesis. See e.g., Folkman, *N. Engl. J. Med.*, 285: 1182–1186 (1971). The receptors to which VEGF specifically binds are an important and powerful therapeutic target for the regulation and modulation of vasculogenesis and/or angiogenesis and a variety of severe diseases which involve abnormal cellular growth caused by such processes. Plowman, et al., *DN&P*, 7(6):334–339 (1994). More particularly, the KDR/FLK-1 receptor's highly specific role in neovascularization make it a choice target for therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Thus, one aspect of the present invention relates to compounds capable of regulating and/or modulating tyrosine kinase signal transduction including KDR/FLK-1 receptor signal transduction in order to inhibit or promote angiogenesis and/or vasculogenesis, that is, compounds that inhibit, prevent, or interfere with the signal transduced by KDR/FLK-1 when activated by ligands such as VEGF. Although it is believed that the compounds of the present invention act on a receptor or other component along the tyrosine kinase signal transduction pathway, they may also act directly on the tumor cells that result from uncontrolled angiogenesis.

Thus, in one aspect, this invention is directed to compounds that regulate, modulate and/or inhibit vasculogenesis and/or angiogenesis by affecting the enzymatic activity of the KDR/FLK-1 receptor and interfering with the signal transduced by KDR/FLK-1. In another aspect, the present invention is directed to compounds which regulate, modulate and/or inhibit the KDR/FLK-1 mediated signal transduction pathway as a therapeutic approach to the treatment of many kinds of solid tumors including, but not limited to, glioblastoma, melanoma and Kaposi's sarcoma, and ovarian, lung, mammary, prostate, pancreatic, colon and epidermoid carcinoma. In addition, data suggest the administration of compounds which inhibit the KDR/Flk-1 mediated signal transduction pathway may also be used in the treatment of hemangioma, restenosis and diabetic retinopathy.

A further aspect of this invention relates to the inhibition of vasculogenesis and angiogenesis by other receptor-mediated pathways, including the pathway comprising the flt-I receptor.

Receptor tyrosine kinase mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and autophosphorylation. Binding sites are thereby created for intracellular signal transduction molecules which leads to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cel-

lular response, e.g., cell division and metabolic effects to the extracellular microenvironment. See, Schlessinger and Ullrich, *Neuron*, 9:1–20 (1992).

The close homology of the intracellular regions of KDR/FLK-1 with that of the PDGF-β receptor (50.3% homology) and/or the related flt-1 receptor indicates the induction of overlapping signal transduction pathways. For example, for the PDGF-β receptor, members of the src family (Twamley et al., *Proc. Natl. Acad. Sci. USA*, 90:7696–7700 (1993)), phosphatidylinositol-3'-kinase (Hu et al., *Mol. Cell. Biol.*, 12:981–990 (1992), phospholipase cγ (Kashishian & Cooper, *Mol. Cell. Biol.*, 4:49–51 (1993)), ras-GTPase-activating protein, (Kashishian et al., *EMBO J.*, 11:1373–1382 (1992), PTP-ID/syp (Kazlauskas et al., *Proc. Natl. Acad. Sci. USA*, 90:6939–6943 (1993)), Grb2 (Arvidsson et al., *Mol. Cell. Biol.*, 14:6715–6726 (1994)), and the adapter molecules Shc and Nck (Nishimura et al., *Mol. Cell. Biol.*, 13:6889–6896 (1993)), have been shown to bind to regions involving different autophosphorylation sites. See generally, Claesson-Welsh, *Prog. Growth Factor Res.*, 5:37–54 (1994). Thus, it is likely that signal transduction pathways activated by KDR/FLK-1 include the ras pathway (Rozakis et al., *Nature*, 360:689–692 (1992)), the PI-3'-kinase, the src-mediated and the plcγ-mediated pathways. Each of these pathways may play a critical role in the angiogenic and/or vasculogenic effect of KDR/FLK-1 in endothelial cells. Consequently, a still further aspect of this invention relates to the use of the organic compounds described herein to modulate angiogenesis and vasculogenesis as such processes are controlled by these pathways.

Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated and may be treated or prevented by the methods of this invention.

Fibrotic disorders refer to the abnormal formation of extracellular matrices. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. An increased extracellular matrix resulting in a hepatic scar can also be caused by a viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis.

Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases such as glomerulonephritis, diabetic nephropathy and malignant nephrosclerosis as well as such disorders as thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The RTK PDGFR has been implicated in the maintenance of mesangial cell proliferation. Floege et al., *Kidney International*, 43:47S–54S (1993).

Many cancers are cell proliferative disorders and, as noted previously, PKs have been associated with cell proliferative disorders. Thus, it is not surprising that PKs such as, for example, members of the RTK family have been associated with the development of cancer. Some of these receptors, like EGFR (Tuzi et al., *Br. J. Cancer*, 63:227–233 (1991), Torp et al., *APMIS*, 100:713–719 (1992)) HER2/neu (Slamon et al., *Science*, 244:707–712 (1989)) and PDGF-R (Kumabe et al., *Oncogene*, 7:627–633 (1992)) are over-expressed in many tumors and/or persistently activated by autocrine loops. In fact, in the most common and severe cancers these receptor over-expressions (Akbasak and Suner-Akbasak et al., *J. Neurol. Sci.*, 111:119–133 (1992), Dickson et al., *Cancer Treatment Res.*, 61:249–273 (1992), Korc et al., *J. Clin. Invest.*, 90:1352–1360 (1992)) and autocrine loops (Lee and Donoghue, *J. Cell. Biol.*, 118:1057–1070 (1992), Korc et al., supra, Akbasak and Suner-Akbasak et al., supra) have been demonstrated. For example, EGFR has been associated with squamous cell carcinoma, astrocytoma, glioblastoma, head and neck cancer, lung cancer and bladder cancer. HER2 has been associated with breast, ovarian, gastric, lung, pancreas and bladder cancer. PDGFR has been associated with glioblastoma and melanoma as well as lung, ovarian and prostate cancer. The RTK c-met has also been associated with malignant tumor formation. For example, c-met has been associated with, among other cancers, colorectal, thyroid, pancreatic, gastric and hepatocellular carcinomas and lymphomas. Additionally c-met has been linked to leukemia. Over-expression of the c-met gene has also been detected in patients with Hodgkins disease and Burkitts disease.

IGF-R, in addition to being implicated in nutritional support and in type-II diabetes, has also been associated with several types of cancers. For example, IGF-I has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteaga et al., *J. Clin. Invest*, 84:1418–1423 (1989)) and small lung tumor cells (Macauley et al., *Cancer Res.*, 50:2511–2517 (1990)). In addition, IGF-1, while integrally involved in the normal growth and differentiation of the nervous system, also appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., *Cancer Res.*, 53:2475–2478 (1993). The importance of IGF-R and its ligands in cell proliferation is further supported by the fact that many cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes and osteoblasts (the stem cells of the bone marrow)) are stimulated to grow by IGF-1. Goldring and Goldring, *Eukaryotic Gene Expression*, 1:301–326 (1991). In a series of recent publications, Baserga suggests that IGF-R plays a central role in the mechanism of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies. Baserga, *Cancer Res.*, 55:249–252 (1995), Baserga, *Cell*, 79:927–930 (1994), Coppola et al., *Mol. Cell. Biol.*, 14:4588–4595 (1994).

STKs have been implicated in many types of cancer including, notably, breast cancer (Cance, et al., *Int. J. Cancer*, 54:571–77 (1993)).

The association between abnormal PK activity and disease is not restricted to cancer. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque development, Alzheimer's disease, von Hippel-Lindau disease, epidermal hyperproliferation, neurodegenerative diseases, age-related macular degeneration and hemangiomas. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in Insulin-R and IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., *DN&P*, 7:334–339 (1994).

As noted previously, not only RTKs but CTKs including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, blk, hck, fgr, AUR[1], AUR[2] and yrk (reviewed by Bolen et at. *FASEB J.*, 6:3403–3409 (1992)) are involved in the proliferative and metabolic signal transduction pathway and thus could be expected, and have been shown, to be involved in many PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been shown

to be an oncoprotein (pp60 $^{v\text{-}src}$) in chicken. Moreover, its cellular homolog, the proto-oncogene pp60^{c}-sc transmits oncogenic signals of many receptors. Over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of pp60$^{c\ sc}$ which is characteristic of malignant cells but absent in normal cells. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

Similarly, Zap70 has been implicated in T-cell signaling which may relate to autoimmune disorders.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restenosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation. Thus, the compounds of this invention may provide an effective method of preventing such embryo implantation and thereby be useful as birth control agents.

In yet another aspect, the compounds of the instant invention can also be used as anti-infective agents.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

Pharmaceutical Compositions and Use

A compound of the present invention or a physiologically acceptable salt thereof, can be administered as such to a human patient or can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, Pa., latest edition.

Routes of Administration

Suitable routes of administration may include, without limitation, oral, intraoral, rectal, transmucosal or intestinal administration or intramuscular, epicutaneous, parenteral, subcutaneous, transdermal, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, intramuscular, intradural, intrarespiratory, nasal inhalation or intraocular injections. The preferred routes of administration are oral and parenteral.

Alternatively, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a solid tumor, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

Composition/Formulation

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

Pharmaceutical compositions for use in the methods of the present invention may be prepared by any methods of pharmacy, but all methods include the step of bringing in association the active ingredient with the carrier which constitutes one or more necessary ingredients. In particular, pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, syrups, elixirs, gels, powders, magmas, lozenges, ointments, creams, pastes, plasters, lotions, discs, suppositories, nasal or oral sprays, aerosols and the like.

For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such buffers with or without a low concentration of surfactant or cosolvent, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl-pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, cremophor, capmul, medium or long chain mono- di- or triglycerides. Stabilizers may be added in these formulations, also.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insulator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may also be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Many of the PK modulating compounds of the invention may be provided as physiologically acceptable salts wherein the claimed compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium (defined elsewhere herein), salts such as the hydrochloride, sulfate, malate, carbonate, lactate, tartrate, maleate, succinate wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide ($Ca(OH)_2$), etc.).

Dosage

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, i.e., the modulation of PK activity or the treatment or prevention of a PK-related disorder.

More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the PK activity). Such information can then be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the IC_{50} and the LD_{50} (both of which are discussed elsewhere herein) for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1).

Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from in vitro data, e.g., the concentration necessary to achieve 50–90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10–90% of the time, preferably between 30–90% and most preferably between 50–90%. At present, the therapeutically effective amounts of the inventive compounds described herein may range from approximately 25 mg/m^2 to 1000-mg/m^2 perday. Even more preferably 25 mg/m^2 to 150 mg/m^2.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

Packaging

The compositions may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or of human or veterinary administration. Such notice, for example, may be of the labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

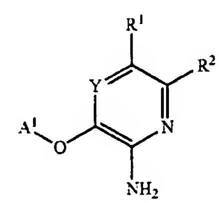
EXAMPLES

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples.

The numbering in the examples corresponds to the numbering in the Tables herein. Reaction schemes and example numbers beginning with a letter (I) relate to pyridine compounds, whereas those beginning with a letter (II) relate to pyrazine compounds. Example numbers beginning with L are library syntheses. Example numbers having a letter notation (a, b, c, etc.) illustrate the synthesis of reagents subsequently used in the synthesis of the inventive compounds, which have a number notation (1, 2, 3, etc.). Reagents can be synthesized as shown herein, or are available from commercial sources (e.g., Aldrich, Milwaukee, Wis.; Acros, Morris Plains, N.J.; Biosynth International, Naperville, Ill.; Frontier Scientific, Logan, Utah; TCI America, Portland, Oreg.; Combi-Blocks, San Diego, Calif.; Matrix Scientific, Columbia, S.C.; Acros, Morris Plains, N.J.; Alfa Aesar, Ward Hill, Mass.: Apollo Scientific, UK; etc.) or can be synthesized by procedures known in the art. When a general or exemplary synthetic procedure is referred to, one skilled in the art can readily determine the appropriate reagents, if not indicated, extrapolating from the general or exemplary procedures.

In the general procedures 1–43 described herein, although some of the procedures are generalized and exemplary, past tense is used to indicate that these general procedures were the procedures used to synthesize the compounds. Some of the general procedures are given as examples for preparing specific compounds. One skilled in the art can readily adapt such procedures to the synthesis of other compounds. It should be understood that R groups shown in the general procedures are meant to be generic and non-limiting, and do not correspond to definitions of R groups elsewhere in this document. Each such R group represents one or multiple chemical moieties that can be the same or different from other chemical moieties also represented by the same R symbol. Moreover, representation of an unsubstituted position in structures shown or referred to in the general procedures is for convenience and does not preclude substitution as described elsewhere herein. For specific groups that can be present, either as R groups in the general procedures or as optional substituents not shown, refer to the descriptions in the remainder of this document, including the claims, summary and detailed description. It should be further understood that compound numbers shown in the general schemes and general procedures in the Examples are for convenient reference only, and do not correspond to the numbers used elsewhere throughout this document. For example, the nitropyridine compound (1) in general scheme I is different from the compound of formula 1

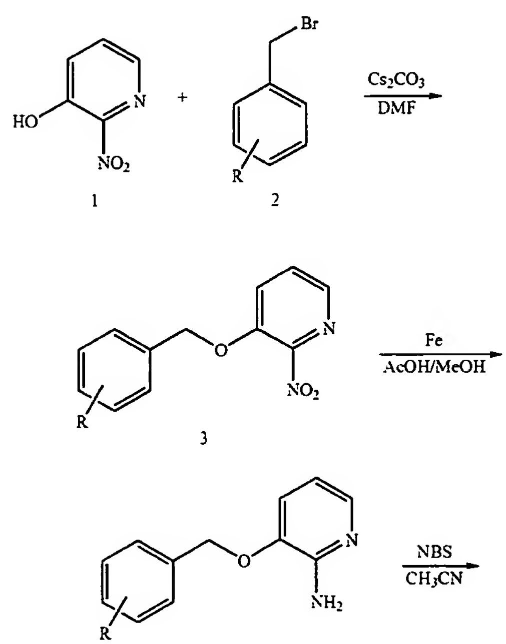
1



described herein.

General Scheme I for the Synthesis of 5-Aryl-3-(Substituted-Benzyloxy)-Pyridin-2-ylamine (6):

General Scheme II for the Synthesis of 5-Aryl-3-(Substituted-Benzyloxy)-Pyrazin-2-ylamine



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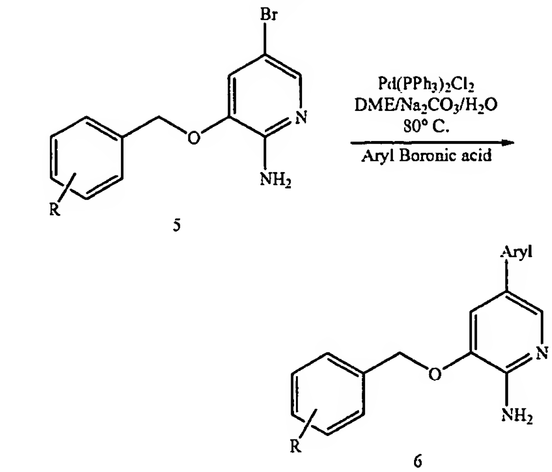
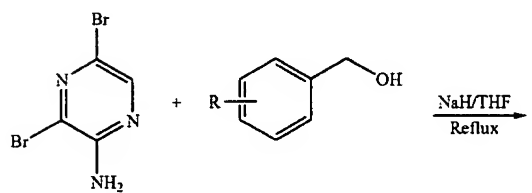
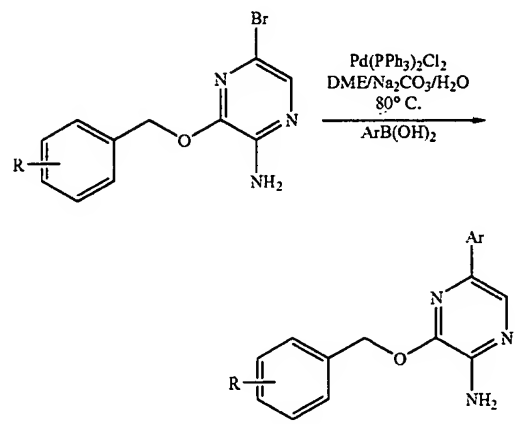


5

6





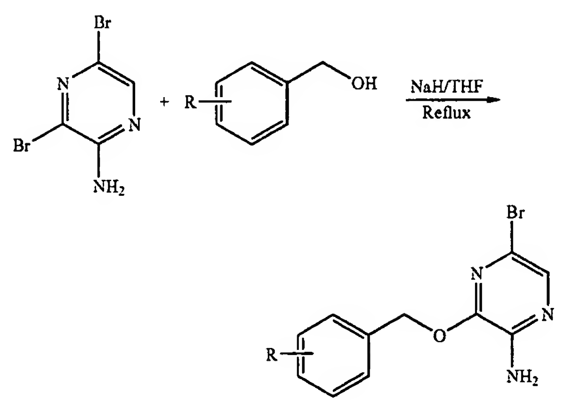
General Procedure 1 for the Synthesis of 5-Bromo-3-(Substituted-Benzyloxy)-Pyridin-2-ylamine (5):

1. Preparation of 3-(substituted-benzyloxy)-2-nitro-pyridine (3): To a stirred solution of Cs_2CO_3 (1.0 molar equivalent)) in DMF (0.2 M) under a N_2 atmosphere containing 3-hydroxy-4-nitro-pyridine (Aldrich, 1.0 molar equivalent) was added substituted benzyl bromide (1.0 molar equivalent). The mixture was stirred for 6 h at ambient temperature. The reaction was then diluted with EtOAc, and partitioned with H_2O. The aqueous layer was extracted with EtOAc twice. The organic layers were then combined, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to dryness under vacuum to yield 3-(substituted-benzyloxy)-2-nitro-pyridine (3) as a solid.

2. Preparation of 3-(substituted-benzyloxy)-pyridin-2-ylamine (4): To a stirred mixture of AcOH and EtOH (1.3:1) was suspended 3-(substituted-benzyloxy-2-nitro-pyridine (1.0 molar equivalent, 1 M) and iron chips (1.0 molar equivalent). The reaction was heated slowly to reflux and allowed to stir for 1 hr. The reaction was cooled to room temperature then filtered through a pad of celite. The resulting filtrate was neutralized with conc. NH_4OH, and then extracted with EtOAc for three times. The combined organic extracts were washed with saturated $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered and concentrated to dryness under vacuum to yield 3-(substituted-benzyloxy)-pyridin-2-ylamine (4) as a solid.

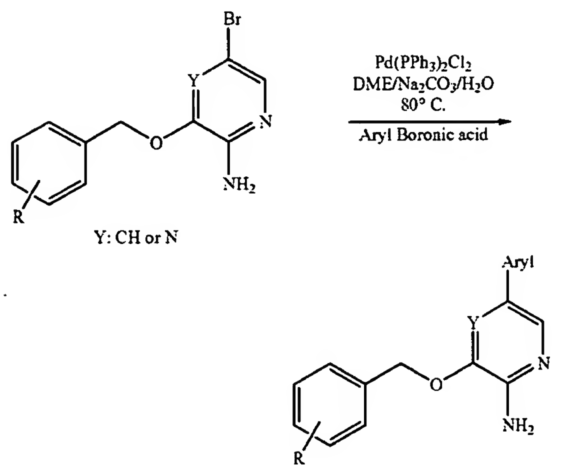
3. Preparation of 5-bromo-3-(substituted benzyloxy)-pyridin-2-ylamine (5): A stirring solution of 3-(substituted-benzyloxy)-pyridin-2-ylamine (4) (1.0 molar equivalent) in acetonitrile was cooled to 0° C. using an ice bath. To this solution was added N-bromosuccinimide (Aldrich, 1.0 molar equivalent) portionwise. The reaction was stirred at 0° C. for 15 min. The reaction was concentrated to dryness under vacuum. The resulting dark oil was dissolved in EtOAc and partitioned with H_2O. The organic was then washed with saturated $NaHCO_3$ twice and brine once. Activated charcoal was added to the organic layer and warmed to reflux. The solution was then cooled to room temperature and filtered through a pad of celite. The organic was then concentrated to dryness under vacuum to one third the original volume. The solids were then filtered off to yield 5-bromo-3-(substituted benzyloxy)-pyridin-2-ylamine (5) as a solid.

General Procedure 2 for the Synthesis of 5-Bromo-3-(Substituted-Benzyloxy)-Pyrazin-2-ylamine.



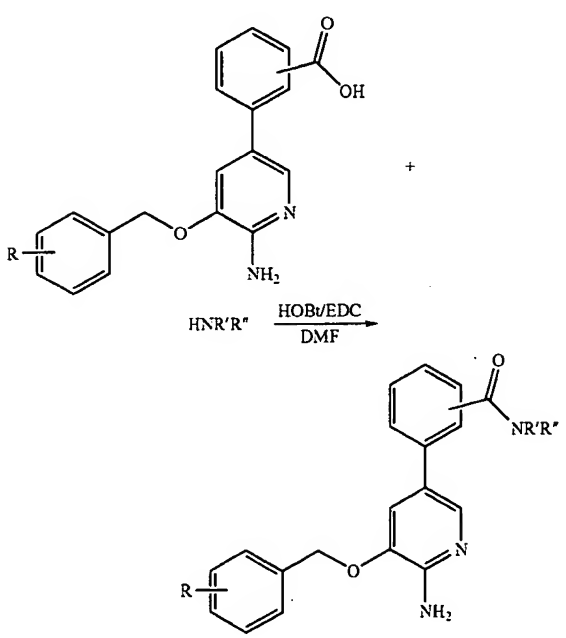
To an ice cooled solution of substituted benzyl alcohol (1.0 molar equivalent) and anhydrous tetrahydrofuran (0.14 M) was added sodium hydride (1.0 molar equivalent) slowly under nitrogen atmosphere. After stirring for 30 minutes, 3,5-dibromopyrazin-2-ylamine (1.0 molar equivalent) in tetrahydrofuran (0.56 M) was added via an addition funnel at a fast dropwise rate. Once the addition was complete the ice bath was removed and the reaction was refluxed under nitrogen and monitored by reversed phase HPLC. After 18 hr HPLC showed that the majority of the starting 3,5-dibromopyrazin-2-ylamine had been consumed and the reaction was allowed to cool to room temperature. The reaction mixture was concentrated, diluted with ethyl acetate, and washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuum. The crude product was purified using a silica gel eluting with 1:1 ethyl acetate/dichloromethane to yield the 5-bromo-3-(substituted-benzyloxy)-pyrazin-2-ylamine as a white solid in 60–90% yield.

General Procedure 3 for the Synthesis of 5-Aryl-3-(Substituted-Benzyloxy)-Pyridin-2-ylamine and 5-Aryl-3-(Substituted-Benzyloxy)-Pyrazin-2-ylamine.



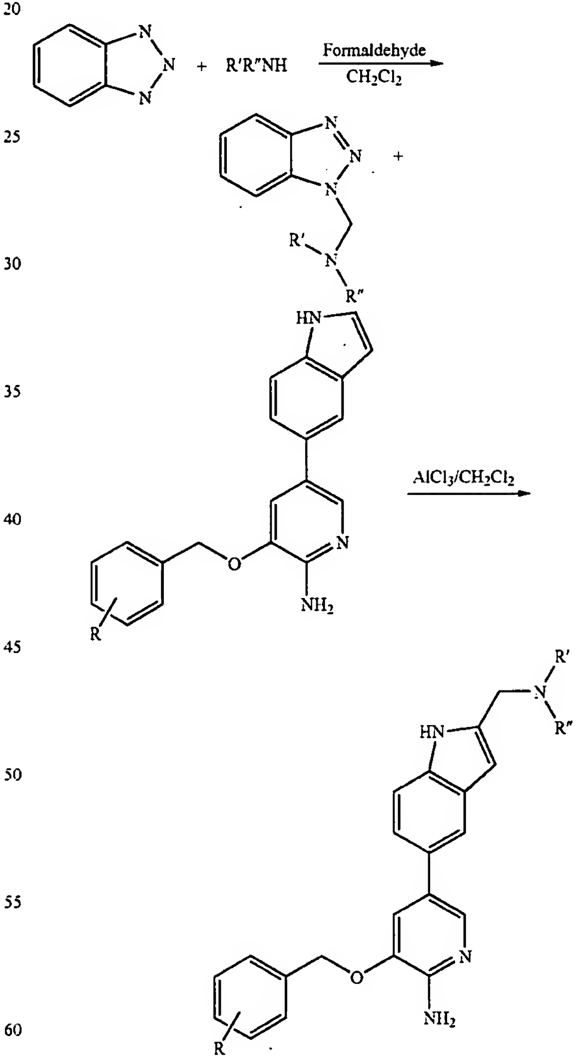
A mixture of 5-bromo-3-(substituted-benzyloxy)-pyridin-2-ylamine or 5-bromo-3-(substituted-benzyloxy)-pyrazin-2-ylamine (1 molar equivalent), aryl boronic acid or ester (1.2 molar equivalent), bis(triphenylphosphine) palladium 11 chloride (0.03 molar equivalent) and sodium carbonate (3.0 molar equivalent) in ethylene glycol dimethyl ether and water (10:0.5, 0.03 M) was de-gassed and charged with nitrogen for three times, and then heated to reflux under nitrogen for overnight. The reaction was cooled to ambient temperature and diluted with ethyl acetate. The mixture was washed with water, brine, dried over Na_2SO_4, and purified on a silica gel column to afford 5-aryl-3-(substituted-benzyloxy)-pyridin-2-ylamine, or 5-aryl-3-(substituted-benzyloxy)-pyrazin-2-ylamine.

General Procedure 4 for Amidation Reaction of 6-amino-5-(substituted-benzyloxy)-pyridin-3-yl]-benzoic acid:



To a solution of 6-amino-5-(substituted-benzyloxy)-pyridin-3-yl]-benzoic acid (1 molar equivalent), 1-hydroxybenzotriazole hydrate (HOBT, 1.2 molar equivalent), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.2 molar equivalent) in DMF (0.2 M) was added amine (1.2 molar equivalent). The reaction solution was stirred at room temperature for overnight, then diluted with EtOAc, and partitioned with H_2O. The organic was separated and the aqueous was extracted with EtOAc. The organic layers were combined, washed with saturated $NaHCO_3$, and concentrated to dryness under vacuum. The material was purified using column chromatography (silica gel, 99:1 to 95:5 CH_2Cl_2/MeOH). The fractions containing product were concentrated under vacuum to yield the amide product.

General procedure 5 for the preparation of 3-(substituted-benzyloxy)-5-(3-dialkylaminomethyl-1H-indol-5-yl)-pyridin-2-ylamine:

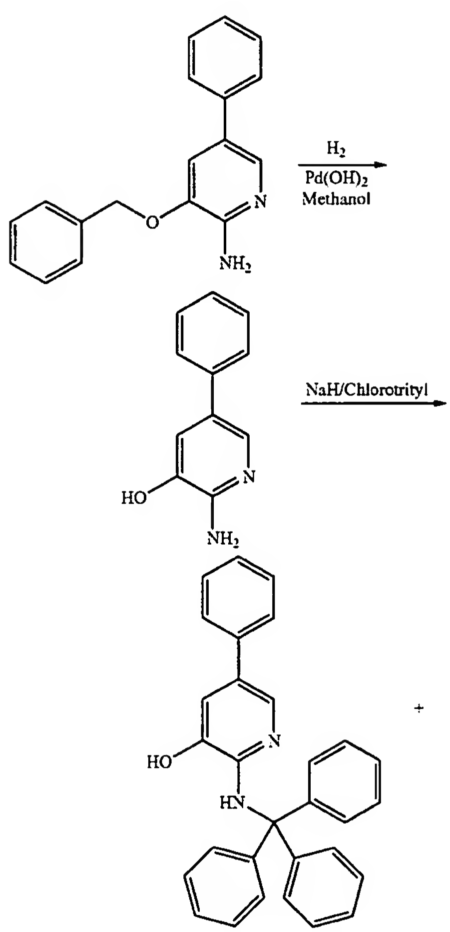


To a solution of benzotriazole (1.0 molar equivalent) in dichloromethane (0.2 M) was added amine (1.0 molar equivalent). The reaction was stirred for 5 minutes at room temperature after which formaldehyde (37% by wt, 1.0 molar equivalent) was added and the reaction was capped

and stirred at room temperature for 3 hr. Once TLC (10% ethyl acetate: dichloromethane) showed the consumption of starting benzotriaziole the reaction was dried with anhydrous magnesium sulfate (10 g), filtered and concentrated in vacuo. The crude product was purified with a silica gel column eluting with 1:1 ethyl acetate: dichloromethane to yield the desired product as a white solid.

To a solution of the aminomethylbenzotriazole intermediate (1.0 molar equivalent) in dichloromethane (0.43 M) was added aluminum chloride (2.0 molar equivalent), and then followed by 3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridine-2-ylamin (1.1 molar equivalent). The reaction was capped and heated with stirring to 40° C. for 3–4 hr. The reaction was then removed from the heat and allowed to cool to room temperature. The reaction mixture was diluted with sodium hydroxide (0.2 M) and chloroform, recapped and vigorously stirred at room temperature to dissolve the residue in the vial. The chloroform was extracted away from the aqueous, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified with a silica gel column, first eluting with 1:1, ethyl acetate: dichloromethane, to elute the less polar impurities and then eluting the product with 90:9:1, chloroform:methanol:ammonium hydroxide. (Yields 10–67%.)

General Procedure 6 for the synthesis of 3-(Substituted-benzyloxy)-5-phenyl-pyridin-2-ylamine using example 1-88:



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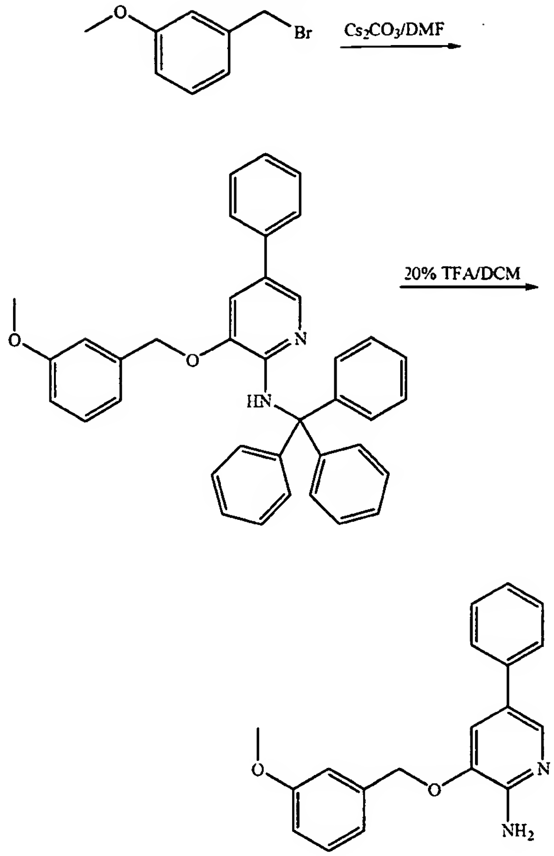


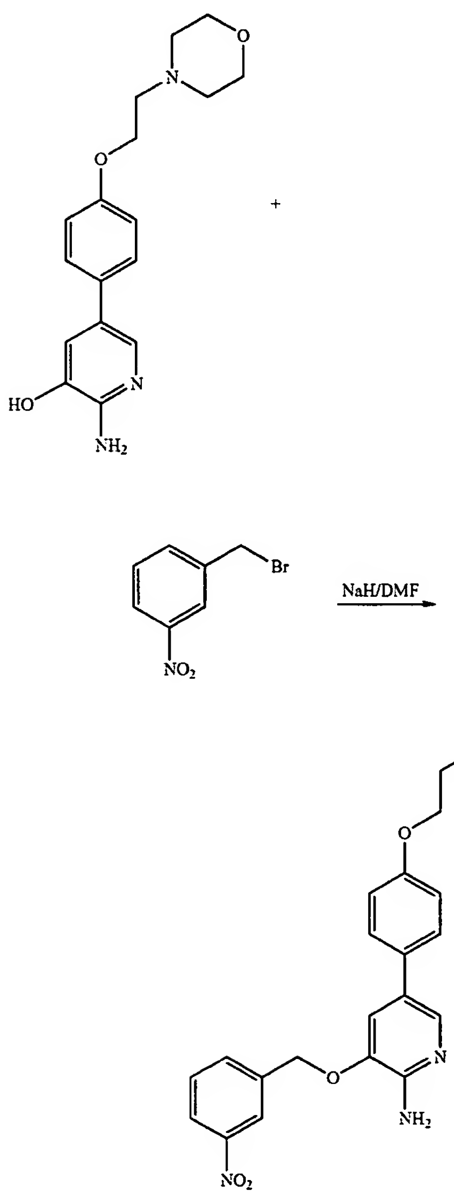
To a solution of 3-benzyloxy-5-phenyl-pyridin-2-ylamine (Example I-87, 3.27 g, 11.8 mmol) in methanol (30 mL) was added $Pd(OH)_2$ (2.5 g, 2.37 mmol). The mixture was degassed and charged with hydrogen three times, and then stirred under hydrogen balloon for 5 hr. The reaction was filtered through a celite pad, washed with methanol, and condensed. After high vacuum dry, 2-amino-5-phenyl-pyridin-3-ol was obtained (2.04 g, 93% yield). MS m/z 187 [M+1].

To a solution of 2-amino-5-phenyl-pyridin-3-ol (2.04 g, 10.95 mmol) in THF (anhydrous, 30 mL) was added NaH (1.31 g, 32.85 mmol) slowly. The mixture was stirred under nitrogen for 20 minutes, and then trityl chloride (3.66 g, 13.14 mmol) was added. The reaction was stirred at room temperature for over night under nitrogen. The solvent was evaporated, and the residue was dissolved in dichloromethane, washed with water, and dried over Na_2SO_4. After filtration and condensation, the crude product was purified on a silica gel column eluting with EtOAc-Hexane (1:10) to provide 5-phenyl-2-(trityl-amino)-pyridin-3-ol (1.09 g, 23% yield). MS m/z 427 [M+1].

To a solution of 5-phenyl-2-(trityl-amino)-pyridin-3-ol (100 mg, 0.24 mmol) in THF (3 mL) was added Cs_2CO_3 (79 mg, 0.24 mmol). The mixture was stirred at room temperature for 20 minutes, and then 3-methoxybenzylbromide (0.037 mL, 0.26 mmol) was added. The reaction was stirred at room temperature overnight, diluted with dichloromethane (5 mL), and filtered to remove the salts. The solvents were evaporated, and the residue was dissolved in 10% trifluoroacetic acid in dichloromethane (2 mL). The

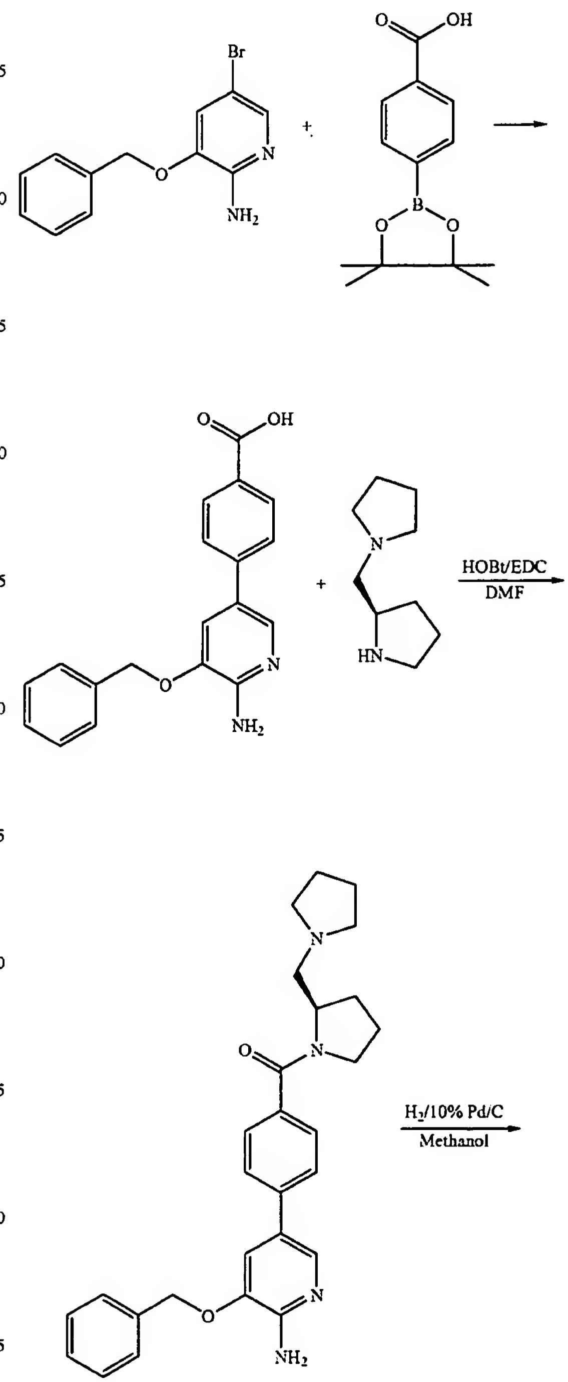
reaction was stirred for 2 hr, and evaporated. The residue was dissolved in dichloromethane, washed by sat. $NaHCO_3$, and dried over Na_2SO_4. After filtration and concentration, the crude product was purified on a silica gel column eluting with methanol-dichloromethane (from 3% to 15% gradient) to provide 3-(3-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine as a white solid (43.5 mg, 60% yield).

General Procedure 7 for the Synthesis of 3-(Substituted-benzyloxy)-5-Aryl-pyridin-2-ylamine using Example I-106:



To a solution of 2-amino-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-3-ol (prepared according to the procedures for 2-amino-5-phenyl-pyridin-3-ol in Example I-88) (45.5 mg, 0.14 mmol) in DMF (3 mL) at 0° C. was added NaH (60% in oil) (5.6 mg, 0.14 mmol) and the mixture was stirred at 0° C. for 20 min. Then 1-Bromomethyl-3-nitro-benzene was added and the mixture was stirred at 0° C. for 1 hr and at room temperature for 2 hr. Cold 1 N aqueous HCl (0.1 mL) was added and the solvent was removed under reduced pressure. The residue was purified with silica gel chromatography (CH_2Cl_2:MeOH:NH_4OH=100:3:0.3) to give 5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-3-(3-nitro-benzyloxy)-pyridin-2-ylamine as yellow solid (44 mg, 68%).

General Procedure 8 for the Synthesis of {4-[6-Amino-5-(substituted-benzyloxy)-pyridin-3-yl]-phenyl}[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone using Example I-111:



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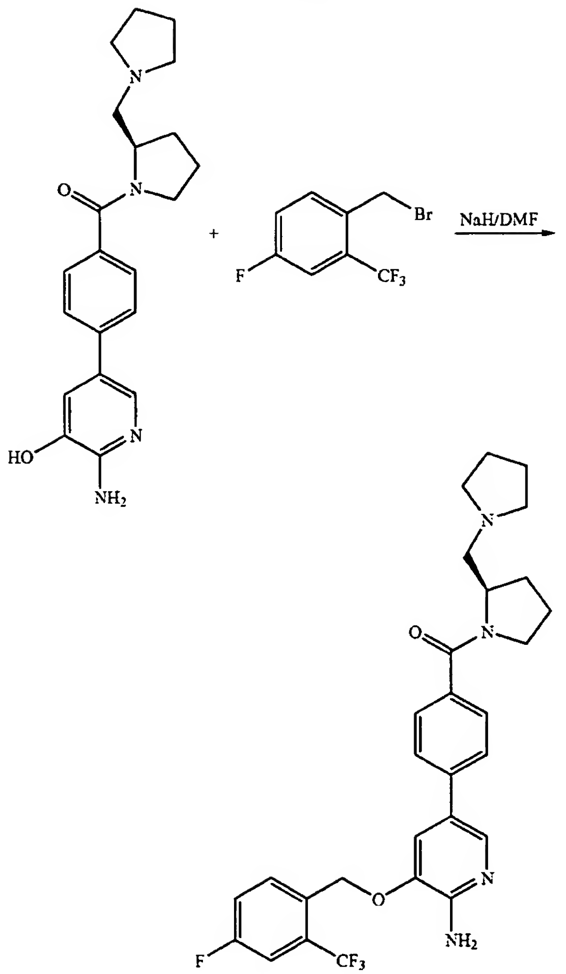


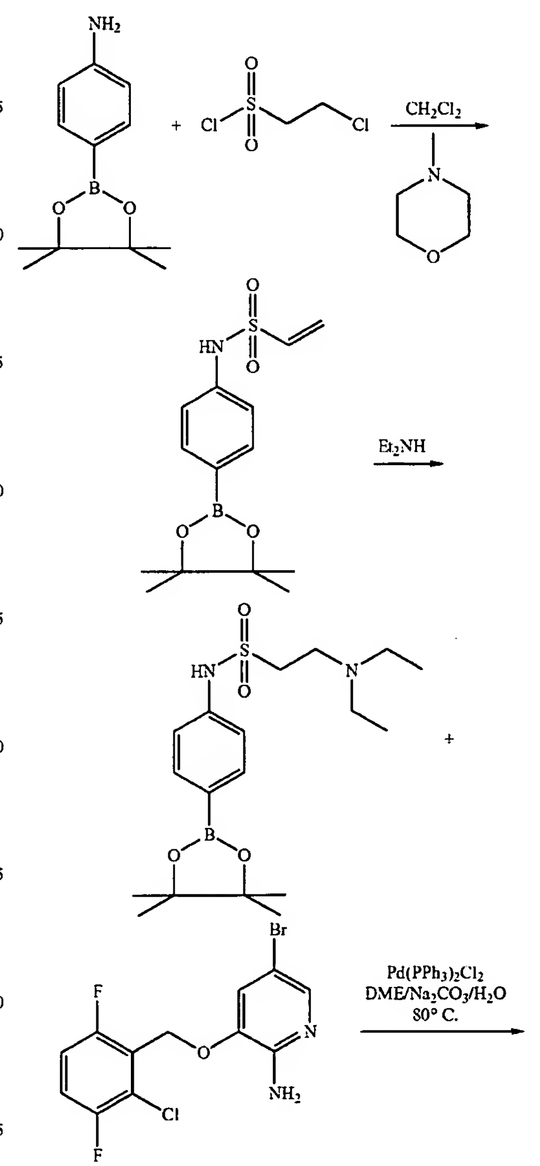
1. 6-Amino-5-benzyloxy-nicotinic acid was prepared according to procedure 3 from 3-benzyloxy-5-bromo-pyridin-2-ylamine and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid. MS m/z 321 (M+1).

2. [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared following procedure 4 using 6-amino-5-benzyloxy-nicotinic acid and (2R)-pyrrolidin-1-ylmethyl-pyrrolidine (prepared in Example I-39). MS m/z 457 (M+1).

3. To a solution of [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-[(2R)-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone (2.28 g, 5.00 mmol) in methanol (25 mL) was added 10% Pd/C (100 mg). The mixture was degassed and charged with hydrogen for three times, and then stirred under hydrogen balloon overnight. The reaction was filtered through a celite pad, washed with methanol, and condensed. After high vacuum dry, [4-(6-amino-5-hydroxy-pyridin-3-yl)-phenyl]-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone was obtained (1.74 g, 95% yield). ^{1}H NMR(400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.54 (m, 3H), 7.46 (m, 2H), 7.14 (s, 1H), 5.68 (s, 2H), 4.22 (m, 1H), 3.45 (m, 2H), 2.66 (m, 1H), 2.52 (m, 4H), 1.96 (m, 2H), 1.84 (m, 3H), 1.64 (m, 4H); MS m/z 367 (M+1).

4. To a stirred solution of [4-(6-amino-5-hydroxy-pyridin-3-yl)-phenyl]-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone (100 mg, 0.27 mmol) in anhydrous DMF(15 mL) under a N_2 atmosphere containing, at 0° C., sodium hydride (60% dispersion in mineral oil, 11 mg, 0.49 mmol) was added. The mixture was allowed to stir at 0° C. for 30 min. 1-(Bromomethyl)-4-fluoro-2-(trifluoromethyl)benzene (0.046 mL, 0.27 mmol) was added. The mixture was stirred at room temperature for 2 hr. The reaction was diluted with EtOAc, and partitioned with H_2O. The aqueous layer was extracted with EtOAc (2x25 mL). The organic layers were combined, washed with H_2O (1x15 mL), brine (1x15 mL), dried over $MgSO_4$, filtered, concentrated, and purified on a silica gel column to yield {4-[6-amino-5-(4-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone as off-white crystals.

General Procedure 9 for the Synthesis 2-Dialkylamino-ethanesulfonic acid [6-amino-5-(substituted-benzyloxy)-pyridin-3-yl]-phenyl-amide using Example I-243.



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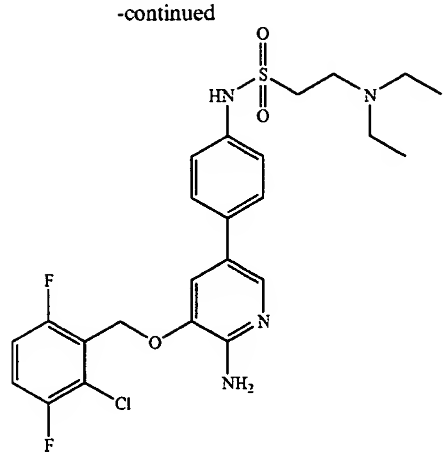


1. To a solution of 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (5 g, 22.8 mmol) in dichloromethane (120 mL) was added N-methyl morpholine (7.5 mL, 68.4 mmol). This mixture was cooled to 0° C. under nitrogen atmosphere. 2-Chloroethanesulfonyl chloride (2.5 mL, 23.9 mmol) in dichloromethane (60 mL) was then added drop wise with stirring. Once the addition was complete the flask was stirred at 0° C. for 1 hr and then at room temperature while monitoring by TLC (1:1 ethyl acetate: hexanes) and staining with ninhydrin. After 4 h stirring some starting boronic ester still remained and an additional 0.2 equivalents (0.5 mL) of 2-chloroethanesulfonyl chloride in dichloromethane (25 mL) was added drop wise at room temperature. After 1 hr the boronic ester had been consumed as shown by TLC and the total reaction volume was reduced by one-half via rotary evaporation. The contents were diluted with ethyl acetate (200 mL), washed with 50% brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated in vacuum. The crude product was purified using silica gel (120 g) and eluting with 10% ethyl acetate, dichloromethane to yield ethenesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amidea as a white solid (6.2 g, 20.2 mmol, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.76 (d, J=8.4, 2H), 7.12 (d, J=8.45, 2H) 6.65 (s, 1H), 6.55 (dd, J=9.77, 6.7, 1H), 6.31 (d, J=16.54, 1H), 5.96 (d, J=9.8, 1H), 1.33 (s, 12H).

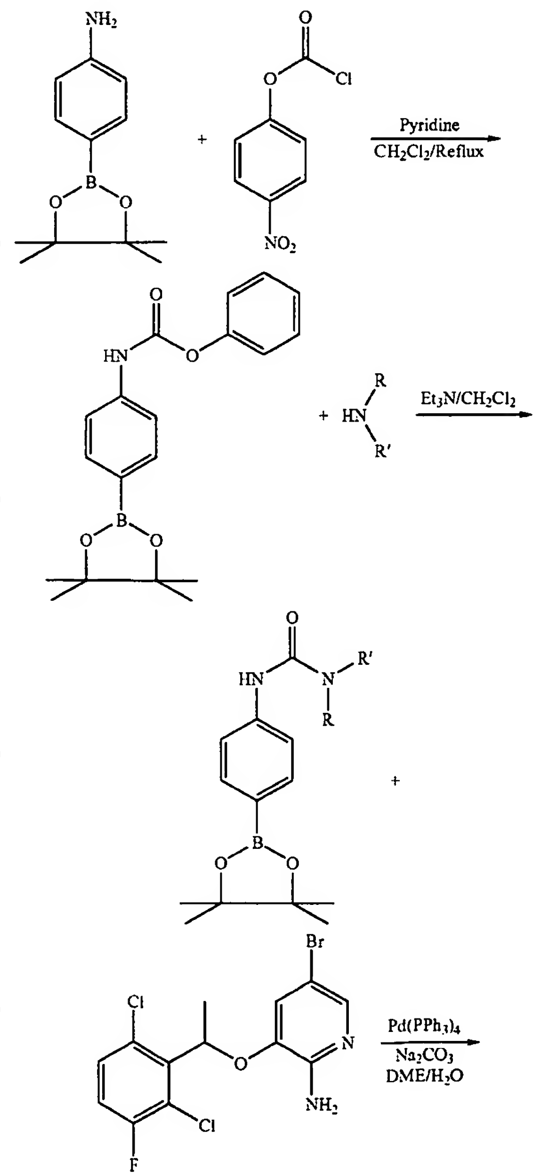
2. To a solution of ethenesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (0.500 g, 1.6 mmol) in methanol (5 mL) was added diethylamine (0.707 g, 4.0 mmol) in methanol (5 mL), and the reaction was stirred at room temperature and monitored by TLC (1:1 Ethyl acetate:hexanes). After 2 hr the reaction was concentrated in vacuum and the residue partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate was then washed with 50% brine (1x50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. Crude product was purified using a 10 g prepacked silica gel column, eluting with 1:1 ethyl acetate: dichloromethane to provide 2-diethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide as a white solid (0.346 g, 0.90 mmol, 56%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J=6.65, 2H) 7.15 (d, J=6.66, 2H), 3.20 (m, 2H), 3.0 (m, 2H), 2.55 (q, J=7.15, 7.16 4H), 1.34 (s, 12H), 1.05 (t, J=7.19, 6H).

3. 2-diethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}amide

was prepared following the general Suzuki coupling procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and 2-diethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide prepared in part 2 as a white solid in 60% yield.

General Procedure 10:

1: 4-(4,4,5,5-tetramethyl 1,3,2 dioxaborolan-2-yl) aniline (3 g, 0.013 mol) was dissolved in dichloromethane (350 mL) to which pyridine (1.02 g, 0.013 mol) and 4-nitrophenyl chloroformate was added. The reaction was stirred for 13 hr where TLC analysis showed consumption of all starting materials. The solution was washed with saturated $NaHCO_3$ (3x50 mL), water (3x50 mL) and brine (3x50 mL). The organic layer was dried over Na_2SO_4 and solvent removed to yield a white crystalline solid [4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid phenyl ester, 4.45 g, 91%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.4 (s, 12H), 7.1 (brs, 1H), 7.3 (d, 2H), 7.5 (d, 2H), 7.8 (d, 2H), 8.3 (d, 2H).



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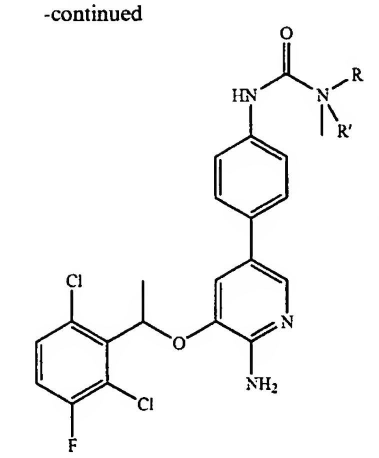
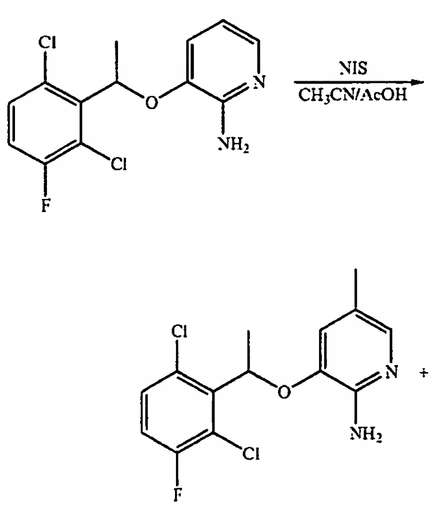


2: [4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-carbamic acid phenyl ester (500 mg, 1.3 mmol) was dissolved in anhydrous dichloromethane (0.5 mL) and triethylamine (0.187 mL, 1.3 mmol). To this stirred solution was added 1-methyl piperazine (or any other amine) (0.144 mL, 1.3 mmol). The solution turned yellow instantly, and tlc analysis showed consumption of all starting material. The reaction was washed with water (3×500 mL), saturated sodium bicarbonate (2×200 mL) and dried prior to removal of solvents in vacuo. The boronic esters were used without purification.

3: To a mixture of 2.1 mL of DME and 2.8 mL of 2N Na_2CO_3 was added 100 mg of the bromide scaffold, 1 equivalent of the boronic acid, and 5 mol % of $Pd(PPh_3)_4$. The reaction was stirred and heated at 80° C. overnight in a two dram vial. The crude mixture was filtered through ceolite and extracted with EtOAc (2×100 mL). The combined extracts were washed with $NaHCO_3$ (1×100 mL), followed by water (1×100 mL), and then saturated brine (1×100 mL). The resulting mixture was concentrated in vacuum. The residue was dissolved in hexane and purified via column chromatography.

General Procedure 11:



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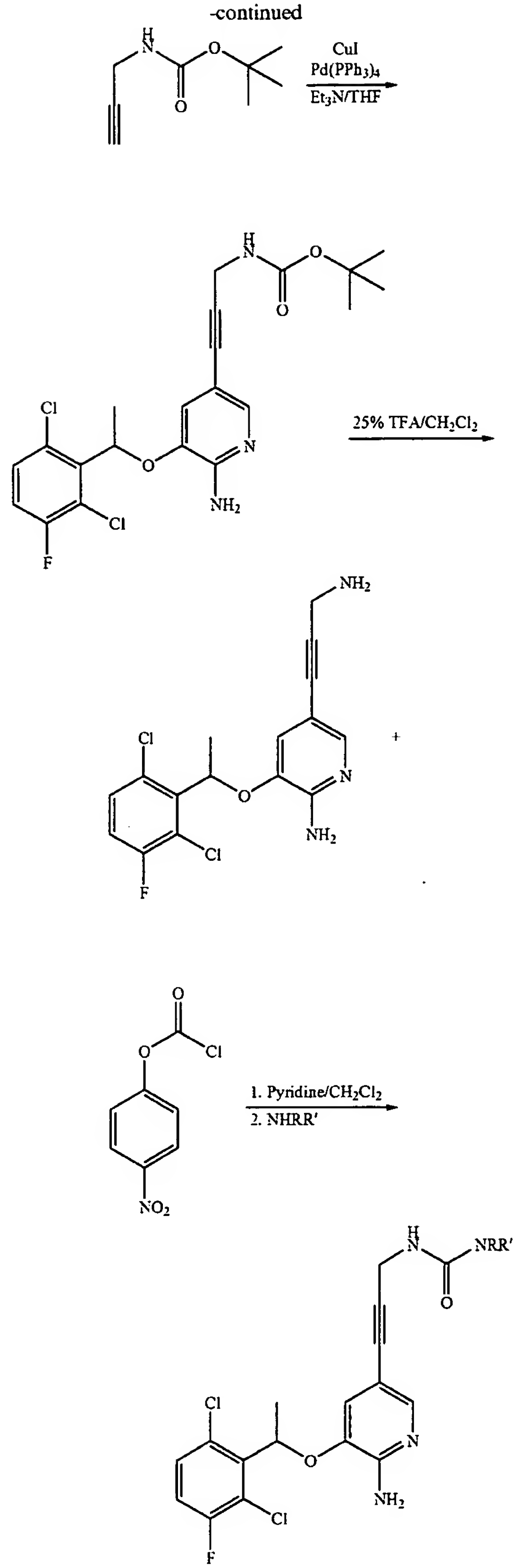


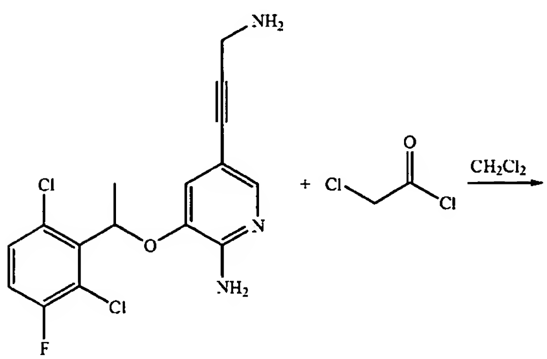
1: To a solution of 3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (10.0 g, 33.2 mmol) in acetonitrile (600 mL) and acetic acid (120 mL) was added N-iodosuccinimide (11.2 g, 49.8 mmol). The mixture was stirred at room temperature for 4 hr and the reaction was quenched with $Na_2S_2O_5$ solution. After evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with 2N NaOH solution, brine, and dried over Na_2SO_4. The crude product was purified on a silica gel column to provide 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-iodo-pyridin-2-ylamine (7.1 g, 50% yield). MS m/z 427 [M+1]

2: To a solution of 3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-iodo-pyridin-2-ylamine (7.1 g, 16.6 mmol) and prop-2-ynyl-carbamic acid tert-butyl ester (3.1 g, 20.0 mmol) in THF (60 mL) and Et_3N (60 mL) was added CuI (63 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (384 mg, 0.3 mmol). The mixture was stirred under nitrogen and monitored by TLC until the reaction was complete. The mixture was extracted with EtOAc and washed by water. The crude product was purified on a silica gel column eluting with 20–40% EtOAc in hexanes to provide (3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-prop-2-ynyl)-carbamic acid tert-butyl ester (2.2 g, 29% yield).

3: The solution of (3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-carbamic acid tert-butyl ester in 25% TFA in dichloromethane was stirred for 2 hr, then washed by 2N NaOH, water twice, brine, dried over Na_2SO_4. After filtration and evaporation, 5-(3-amino-prop-1-ynyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine was obtained in 93% yield.

4: To a solution of 5-(3-amino-prop-1-ynyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (0.282 mmol, 1 eq) and 4-nitrophenyl chloroformate (1 eq) in anhydrous dichloromethane (10 mL) was added pyridine (1 eq). The reaction was stirred for 4 hr under nitrogen, and then the selected amine (1 eq) and triethylamine (1 eq) were added. The mixture was refluxed for 5 minutes and cooled to room temperature. The reaction mixture was washed with water. The organic layer was evaporated and purified on a silica gel column eluting with 0–20% methanol in dichloromethane on prepacked silica columns. Final yields varied between 24% and 71%.

General Procedure 12:



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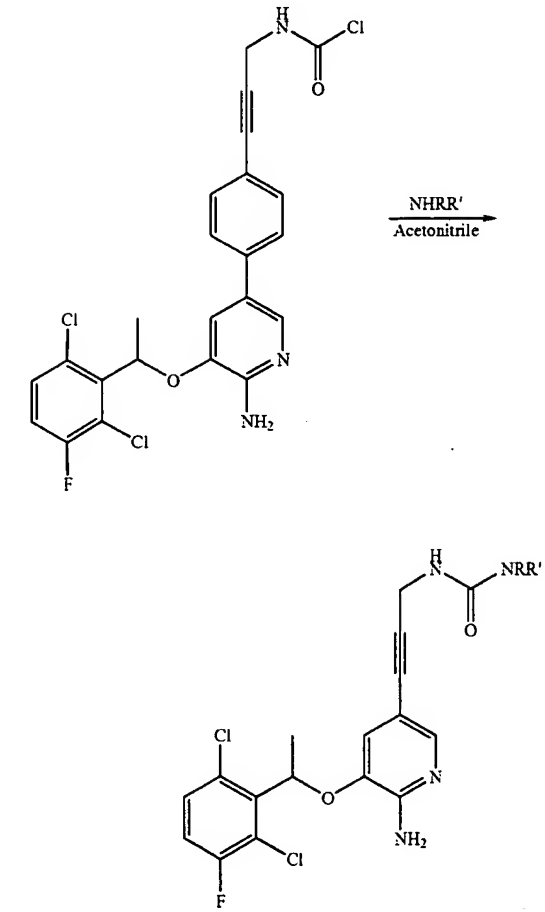
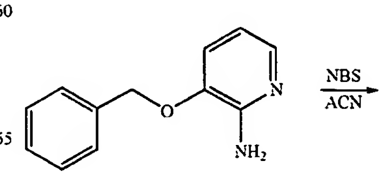


1: To a solution of 5-(3-amino-prop-1-ynyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (prepared in procedure 11) (400 mg, 1.1 mmol) in dichloromethane (17 mL) was added chloroacetyl chloride (153 mg, 1.4 mmol). The reaction was stirred at room temperature with TLC monitor of the completion of the reaction. After the completion, the solvent was evaporated to get the crude product.

2: To a solution of N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-prop-2-ynyl)-2-chloro-acetamide (1 eq) in acetonitrile (5 eq) was added the individual amine (5 eq). The mixture was refluxing under nitrogen overnight. After evaporation of solvent, the residue was purified on a silica gel column eluting with 1–10% methanol in dichloromethane to provide the product with yields varied between 47% to 97%.

General Procedure 13:



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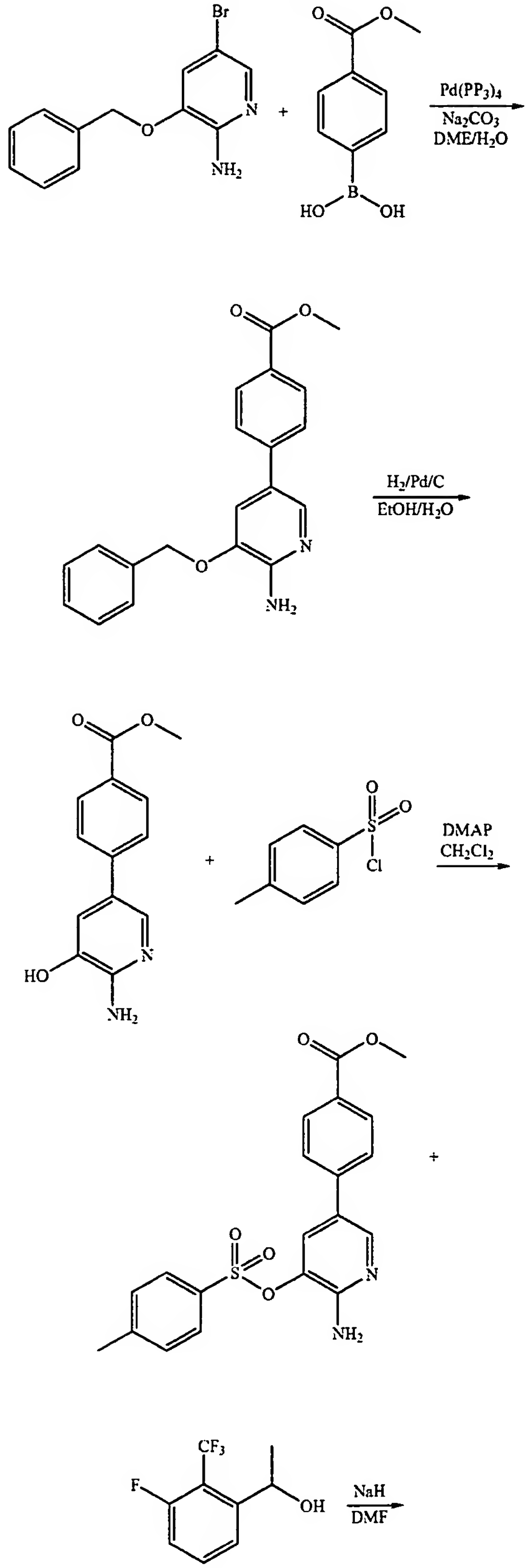

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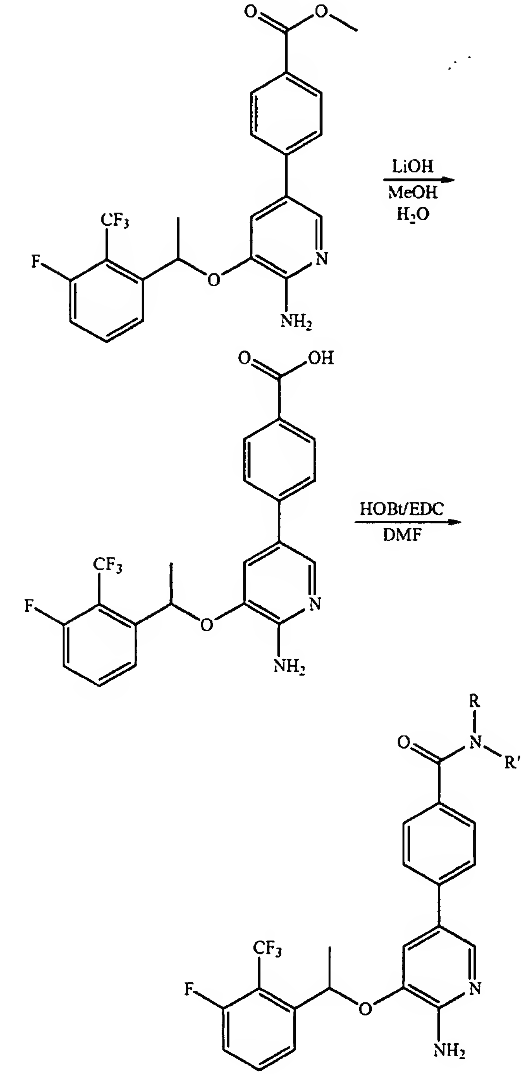


1. To a stirred solution of 2-amino-3-benzyloxypyridine (42.0 g, 0.21 mol) in CH_3CN (600 mL) at 0° C. was added N-bromosuccinimide (37.1 g, 0.21 mol) over 30 minutes. The mixture was stirred for 0.5 hr, after which the reaction was then diluted with EtOAc (900 mL) and partitioned with H_2O (900 mL). The organic layer was washed with brine and dried (Na_2SO_4), filtered and concentrated to dryness under vacuum to yield 3-benzyloxy-5-bromo-pyridin-2-ylamine (31.0 g, 0.11 mol, 53%). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.63–4.78 (brs, 2H), 5.04 (s, 2H), 7.07 (d, 1H, J, 1.8 Hz), 7.33–7.42 (m, 5H), 7.73 (d, 1H, J, 1.8 Hz).

2. To a stirred mixture of 3-benzyloxy-5-bromo-pyridin-2-ylamine (31.0 g, 0.11 mol) in a mixture of DME (600 mL) and H_2O (600 mL) was added 4-carboxymethylboronic acid (29.9 g, 0.11 mol), $Pd(PPh_3)_4$ (6.4 g, 5.55 mmol), and Na_2CO_3 (82.0 g, 0.78 mol). The reaction was heated slowly to reflux and allowed to stir for 3 hr. The reaction was cooled to room temperature, then diluted with CH_2Cl_2 (1.5 L) and partitioned with H_2O (700 mL). The organic layer was washed with saturated $NaHCO_3$ (700 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was

purified by column chromatography (silica gel, 1:1 to 4:1 EtOAc:hexanes) and the fractions containing product were combined and concentrated in vacuo to yield 4-(6-amino-5-benzyloxy-pyridin-3-yl)-benzoic acid methyl ester (29.4 g, 0.086 mol, 79%). [1]H NMR ($CDCl_3$, 300 MHz) δ 3.92 (s, 3H), 4.82–4.94 (brs, 2H), 5.15 (s, 2H), 7.22 (d, 1H, J, 1.8 Hz), 7.33–7.42 (m, 5H), 7.54 (d, 2H, J, 8.6), 7.98 (d, 1H, J, 1.8 Hz), 8.06(d, 2H, J. 8.6 Hz).

3. To a stirring solution of 4-(6-amino-5-benzyloxy-pyridin-3-yl)-benzoic acid methyl ester (10.0 g, 0.03 mol) in EtOH:H_2O (95:5, 600 mL) was added Pd/C (15.9 g, 0.015 mol) (the reaction was de-gassed under vacuum). The solution was allowed to stir under an H_2 atmosphere for 22 hr. The solution was filtered through wet celite and the celite washed with EtOH. The filtrate was concentrated under vacuum to yield 4-(6-Amino-5-hydroxy-pyridin-3-yl)-benzoic acid methyl ester (2.3 g, 9.3 mmol, 31%). [1]H NMR (MeOD, 300 MHz) δ 3.90 (s, 3H), 7.21 (d, 1H, J, 1.9 Hz), 7.62 (d, 2H, J, 8.5 Hz), 7.76 (d, 1H, J, 1.9 Hz), 8.04(d, 2H, J, 8.5 Hz).

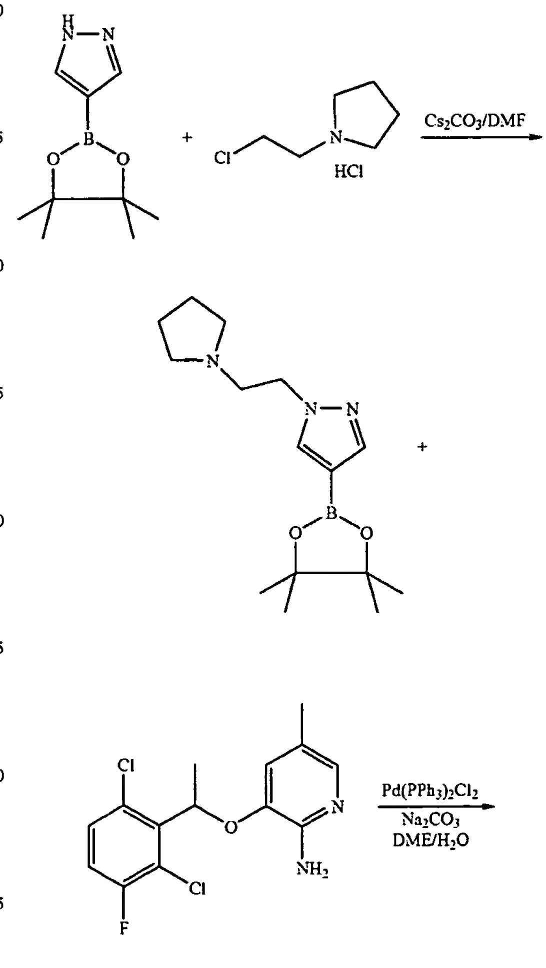
4. To a stirring solution of 4-(6-amino-5-hydroxy-pyridin-3-yl)-benzoic acid methyl ester (2.3 g, 9.3 mmol) in CH_2Cl_2 (180 mL) was added N,N-diisopropylethylamine (3.2 mL, 0.019 mol), 4-methyl-benzenesulfonyl chloride (2.66 g, 0.014 mol), and PS-DMAP (catalytic amount). The reaction was stirred at ambient temperature for 6 hr then filtered to remove the resin. The resin was washed with CH_2Cl_2 (3×20 mL), and the combined fractions were washed with 10% citric acid (100 mL), saturated NaCl (100 mL), dried (Na_2SO_4) and filtered and concentrated in vacuo. The resulting crude material was purified by column chromatography (silica gel, 100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH) and the fractions containing the desired product were combined and concentrated in vacuo to yield 4-[6-Amino-5-(toluene-4-sulfonyloxy)-pyridin-3-yl]-benzoic acid methyl ester (3.3 g, 8.2 mmol, 88%). [1]H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 3.93 (s, 3H), 4.81–4.88 (brs, 2H), 7.36–7.44 (m, 5H), 7.81 (d, 2H, J, 8.3 Hz), 8.05 (d, 2H, J, 8.4 Hz), 8.19–8.27 (brs, 1H).

5. To a stirred solution of 1-(3-fluoro-2-trifluoromethyl-phenyl)-ethanol (2.0 g, 9.6 mmol) in anhydrous DMF (500 mL) at 0° C. under a N_2 atmosphere was added NaH (0.38 g, 9.6 mmol). The reaction was allowed to stir for 0.5 hr. A solution of 4-[6-Amino-5-(toluene-4-sulfonyloxy)-pyridin-3-yl]-benzoic acid methyl ester (3.8 g, 9.6 mmol) in anhydrous DMF (30 mL) was added to the reaction mixture which was allowed to come to ambient temperature slowly and stirred for 21 hr at this temperature. The reaction was diluted with EtOAc (500 mL) and H_2O (100 mL). The organic layer was separated off and the aqueous was further extracted with EtOAc (1×200 mL). The organic layers were combined and washed with brine (1×100 mL), dried with Na_2SO_4 and concentrated to dryness under vacuum. The crude mixture was purified by column chromatography (silica gel, 40:60 to 70:30 EtOAc:hexanes) and the fractions containing product were combined and concentrated in vacuo to yield 4{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid methyl ester (1.4 g, 3.2 mmol, 34%). [1]H NMR ($CDCl_3$, 300 MHz) & 1.73 (d, 3H. J. 6.2 Hz), 3.91 (s, 3H), 4.87–4.64 (brs, 2H), 5.81 (q, 1H, J, 6.1, 6.3 Hz), 6.92 (d, 1H, J, 1.8 Hz), 7.38 (d, 2H, J, 8.5 Hz), 7.46–7.66 (m, 3H), 7.93 (d, 1H, J, 1.8 Hz), 8.02 (d, 2H, J, 8.5 Hz).

6. To a stirred solution of 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid methyl ester (1.4 g, 3.2 mmol) in warm IPA (72 mL) was added H_2O (38 mL) containing LiOH (0.68 g, 16.2 mmol). The reaction was heated to reflux for 3.5 hr. The reaction was neutralized and diluted with EtOAc (200 mL) and extracted upon cooling. The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to yield 4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl)-benzoic acid (1.2 g, 2.8 mmol, 88%). [1]H NMR (MeOD, 300 MHz) δ 1.75 (d, 3H, J, 6.2 Hz), 4.88–4.93 (m, 1H), 7.01 (d, 1H, J, 1.8 Hz), 7.39 (d, 2H, J, 8.3 Hz), 7.52–7.67 (m, 3H), 7.80 (d, 1H, J, 1.8 Hz), 7.97 (d, 2H, J, 8.3 Hz).

7. Preparation of amide compounds: A stirring solution of 4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid (50 mg, 0.12 mmol), EDC (27.0 mg, 0.13 mmol) and HOBt (18.0 mg, 0.13 mmol) in DMF (2 mL) was added to a two dram vial containing NHR_1R_2 (0.12 mmol). The reaction was stirred at room temperature for 18 hr. The reaction was then diluted with CH_2Cl_2 (3 mL) and partitioned with H_2O. The organic was separated washed with saturated NaCl (1×2 mL) and saturated $NaHCO_3$ (1×2 mL). The organic was concentrated to dryness under vacuum. The material was purified using column chromatography (silica gel, 99:1 to 95:5 CH_2Cl_2/MeOH). The fractions containing product were concentrated under vacuum to yield amide compounds.

General Procedure 14:



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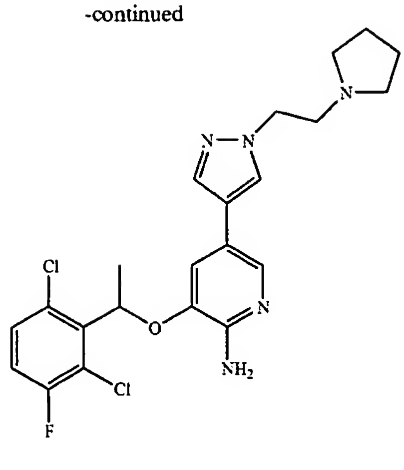
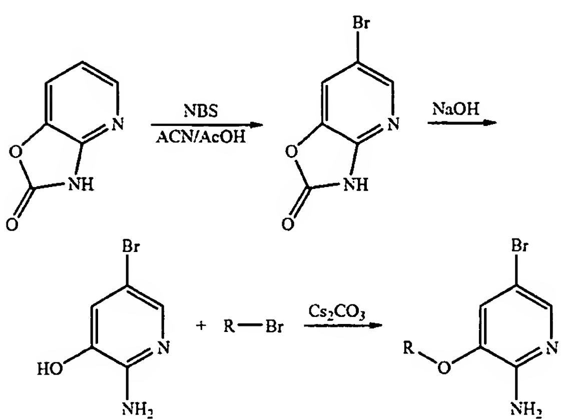


1: To a mixture of 1-(2-chloroethyl)pyrrolidine hydrochloride (200 mg, 1.18 mmol) and 4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)]-1H-pyrazole (229 mg, 1.19 mmol) in DMF (6 mL) was added Cs_2CO_3. The mixture was stirred at room temperature overnight. Water (10 mL) was then added to the mixture. The product was extracted with EtOAc (3×10 mL). The combined extracts were then washed with brine (5×10 mL) to remove the DMF, then dried over Na_2SO_4, and concentrated (142 mg, 41% yield).

2: To a mixture of 3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-iodo-pyridin-2-ylamine (200 mg, 0.468 mmol), pinacol boronic ester (1.2 eq), Na_2CO_3 (149 mg, 1.41 mmol) in water (1.25 mL), and dimethyl ethyl glycol (3.75 mL, 0.1M) was added $Pd(PPh_3)_2Cl_2$ (16 mg, 0.020 mmol) in a microwave reaction vessel. The system was degassed and charged with nitrogen. The mixture was stirred at 160° C. in a microwave apparatus for 15 minutes. The mixture was cooled to room temperature followed by the addition of water (10 mL). The product was extracted with EtOAc (3×20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by reverse phase HPLC with 0.1% TFA in water and acetonitrile.

General Procedure 15:

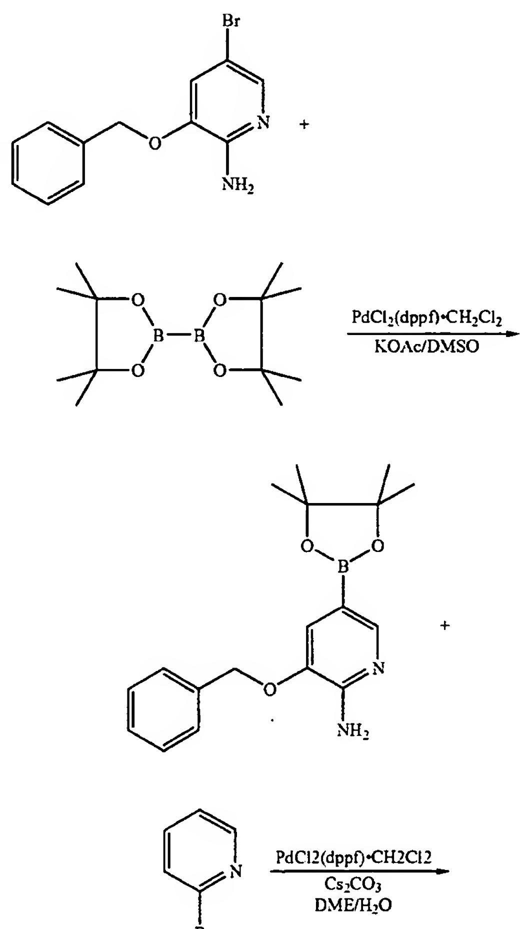


1: To a solution of 3H-oxazolo[4,5-b]pyridin-2-one (13.6 g, 100 mmol) in acetonitrile (600 mL) and acetic acid (120 mL) was added N-bromosuccinimide (21.4 g, 120 mmol). The mixture was stirred at room temperature for 4 hr and the reaction was quenched with $Na_2S_2O_5$ solution. After evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was washed with 2N NaOH solution, brine, and dried over Na_2SO_4. The crude product was purified on a silica gel column to provide 6-bromo-3H-oxazolo[4,5-b]pyridin-2-one (11.5 g, 55% yield).

2: 6-Bromo-3H-oxazolo[4,5-b]pyridin-2-one (21.5 g, 100 mmol) was suspended in NaOH solution (2N, 250 mL, 500 mmol). The mixture was refluxed overnight and a clear solution was obtained. After cooling to room temperature, the reaction solution was neutralized to pH ~7. A lot of CO_2 was released and also precipitate was observed. The product was filtered, washed with water, and dried under high vacuum to provide 2-amino-5-bromo-pyridin-3-ol as an off-white solid (17.8 g, 98% yield).

3: To a solution of 2-amino-5-bromo-pyridin-3-ol (358 mg, 1.89 mmol) in DMF (8 mL) was added Cs_2CO_3 (620 mg, 1.89 mmol). The mixture was stirred at room temperature under nitrogen for 1 hr. To the reaction mixture was added bromo-compound (0.9 eq) in DMF (5 mL) slowly. The reaction solution was stirred under nitrogen for five hr, and then partitioned between water and ethyl acetate. The organic layer was washed with brine for three times, dried over $MgSO_4$. The crude product was purified on a silica gel column eluting with hexane-ethyl acetate (4:1) to provide the product with 70%–80% yield.

General Procedure 16 using Example I-488:



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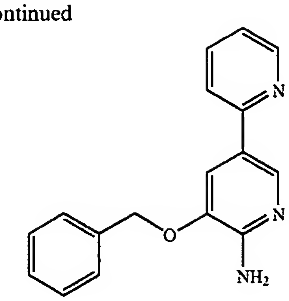
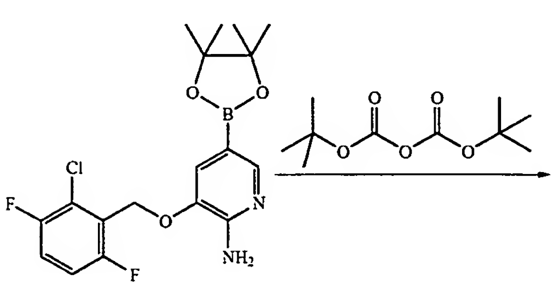


1. To a solution of 3-benzyloxy-5-bromo-pyridin-2-ylamine (1 g, 3.58 mmol) in dimethylsulfoxide (7 mL) was added sequentially bis(pinacolato)diborane (1.0 g, 3.94 mmol), potassium acetate (1.05 g, 10.7 mmol) [1,1'-bis(diphenylphosphino)ferrocine]dichloropalladium (II), complex with dichloromethane (1:1) (146 mg, 0.18 mmol). The mixture was heated to 80° C. for 16 hr and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was washed with water (2×50 mL) and dried over magnesium sulfate. Concentration in vacuo yielded the crude boronate as a brown solid (1.13 g, 97%). ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 12H), 5.08 (s, 2H), 5.44 (br s, 2H), 7.33–7.42 (m, 6H), 8.03 (s, 1H).

2. An 18 mL reaction vessel was charged with the crude 3-benzyloxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylamine (161 mg, 0.49 mmol), dimethoxyethane (3 mL) and 2-bromopyridine (117 mg, 0.74 mmol). To this solution was added (1,1'-bis(diphenylphosphino) ferrocine]dichloropalladium (II), complex with dichloromethane (1:1) (20 mg, 0.05 mmol) and a 2 M solution of cesium carbonate in water (0.75 mL, 1.5 mmol). The reactor was warmed to 80° C. for 66 hr under a nitrogen atmosphere, then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (5 mL) and water (5 mL). The organic layer was washed with additional water (5 mL) and diluted with dimethylformamide (5 mL). Polymer-bound sulfonic acid (0.5 g, 2.1 mmol) was added to the organic solution, and the resulting mixture was gently agitated for 2 hr. The resin was filtered and washed with dimethylformamide, methanol and methylene chloride (3×5 mL each solvent). Then the polymer was reacted with 2 M ammonia in methanol for 1 hr. The resin was filtered and washed with additional 2 M ammonia in methanol (2×5 mL), and the combined filtrates were concentrated in vacuo. Purification of the crude product by flash column chromatography yielded 52.2 mg of product as a tan solid (38% yield).

General Procedure 17:



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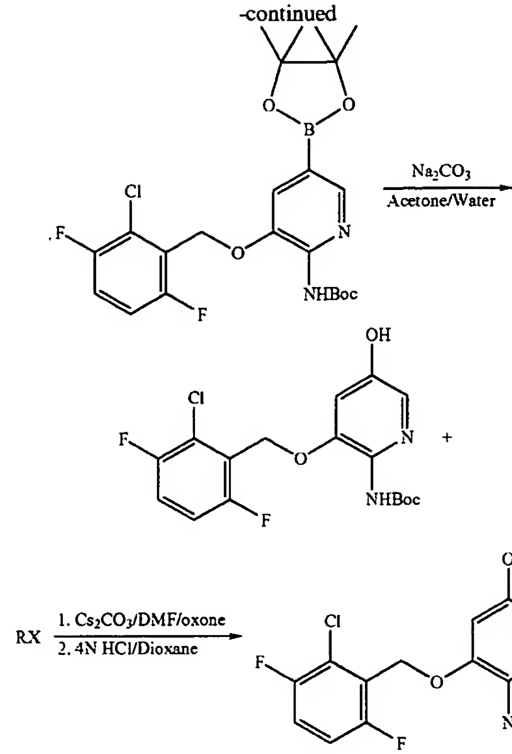


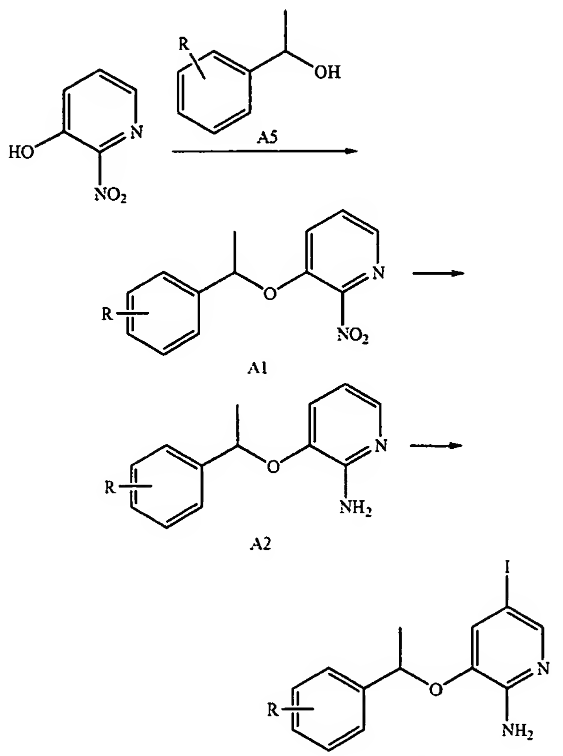
1. To the solution of 3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylamine (procedure 16) (10.0 g, 24.3 mmol) in t-butyl alcohol (50 mL) was added boc anhydride (5.83 g, 26.7 mmol) and reaction stirred at room temperature overnight. Additional boc anhydride (2.25 g, 10.3 mmol) was added and reaction stirred overnight again. Material was concentrated to a viscous black oil and used as-is.

2. The crude boronic ester (24.3 mmol theoretical) in THF (150 mL) was added to a solution of sodium bicarbonate (16.3 g, 194 mmol) in water (150 mL) and acetone (23 mL). The mixture was cooled to 2° C. and oxone (13.5 g, 21.9 mmol) added slowly, keeping temperature below 8° C. Upon completion of addition, reaction was stirred for 5 minutes then quenched with sodium bisulfite (14.2 g) in water (28 mL). Ethyl acetate was added (200 mL) and layers separated. Aqueous layer was neutralized with 6N HCl and extracted with ethyl acetate (2×200 mL). Combined organics were washed with water (250 mL) and brine (250 mL), dried (Na_2SO_4) and concentrated to a crude black oil. Silica gel chromatography (ethyl acetate/hexane) gave the product as a light brown foam (4.78 g, 49.0%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.74 (d, 3H), 5.75 (q, 1H), 6.61 (d, 1H), 76.89 (dt, 1H), 6.94–7.04 (m, 2H), 7.26(d, 1H), 8.19 (bs, 1H). MS m/z 401 $(M+H)^+$.

3. To cesium carbonate in a 2 dram vial was added [3-(2-Chloro-3,6-difluoro-benzyloxy)-5-hydroxy-pyridin-2-yl]-carbamic acid tert-butyl ester (100 mg, 0.25 mmol) in anhydrous DMF (1 mL) followed by benzyl bromide (89.2 μL, 0.75 mmol). The vial was capped and stirred at 90° C. overnight. Reaction was filtered through a 5 mL Chem-Elut tube pre-wetted with water (3.5 mL) and eluted with 1:1 ethyl acetate:methylene chloride. After partial concentration, 4N HCl in dioxane (1–2 mL) was added and solution concentrated. Reverse phase chromatography (water:aceto-

nitrile, 0.05% TFA) followed by lyophilization, gave the desired product as an off white amorphous solid (25.3 mg, 20.0%) and the bis-addition product as a tan amorphous solid (35.2 mg, 23.7%).

General Procedure 18:



Sodium borohydride (1.5 molar equivalent) was added to solution of ketone (3.89 mmol) in 10 mL of ethanol under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 12 hr. The mixture was then put in an ice bath and quenched with dilute aqueous HCl. The ethanol was evaporated and EtOAc was added to extract the aqueous solution. The EtOAc layer was dried over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a oil residue, compound A5. The residue was used without further purification.

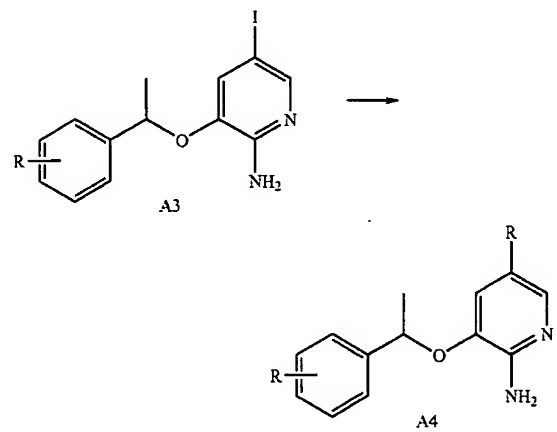
3-Hydroxy-2-nitropyridine (1.1 molar equivalent) and triphenylphosphine (1.5 molar equivalent) were added to a solution of compound A5 (1.1 mmol) in 10 mL of THF. The reaction mixture was then put in an ice bath and diisopropyl azodicarboxylate (1.5 molar equivalent) was added. The ice bath was removed and the mixture was stirred at room temperature for 12 hr. The solvent was evaporated to give a yellow oil residue. The residue was purified by silica gel chromatography (eluting EtOAc in hexanes) to give compound A1.

2 M HCl (0.2 mL) was added to solution of compound A1 (0.97 mmol) in 2 mL of ethanol. The mixture was then put in an ice bath and Fe powder (365 mg) was added slowly. The reaction was heated to 85° C. for 1 hr and cooled to room temperature. Celite (0.5 g) was added to stir and the resulting mixture was filtered through a bed of celite and

rinsed with ethanol. The filtrated was evaporated to give a brown oil residue, compound A2. The residue was used without further purification.

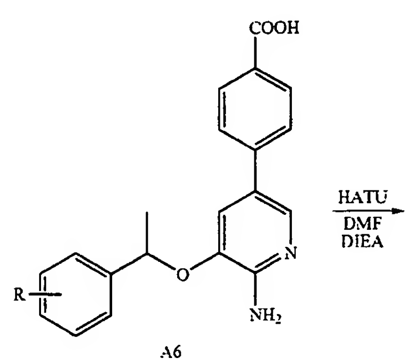
Periodic acid (0.25 molar equivalent), iodine (0.5 molar equivalent), H_2O (0.5 mL), and concentrate sulfuric acid (0.03 mL) were added to a solution of compound A2 in 3 mL of acetic acid. The reaction mixture was heated to 85° C. for 5 hr. The reaction mixture was then cooled in an ice bath and basified with sat. aq. Na_2CO_3 to a pH of 3–4. Ethyl acetate was added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a brown oil residue. The residue was purified by silica gel chromatography (eluting with EtOAc and hexanes) to give desired product, compound A3.

General Procedure 19:



Boronic ester or boronic acid (1.3 molar equivalent) was added to a solution of compound A3 (0.47 mmol) in 5 mL of DME. The mixture was perged with nitrogen several times and then dichlorobis(triphenylphosphino) palladium (II) (0.05 molar equivalent) was added. Sodium carbonate (3 molar equivalent) in 1 mL of H_2O was added to the reaction mixture and the resulting solution was heated to 85° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a dark brown oil residue. The residue-was purified by silica gel chromatography (eluting with CH_3OH, CH_2Cl_2, EtOAc, and hexanes) to give desired product, compound A4.

General Procedure 20:



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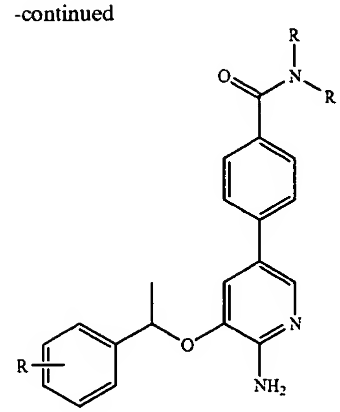
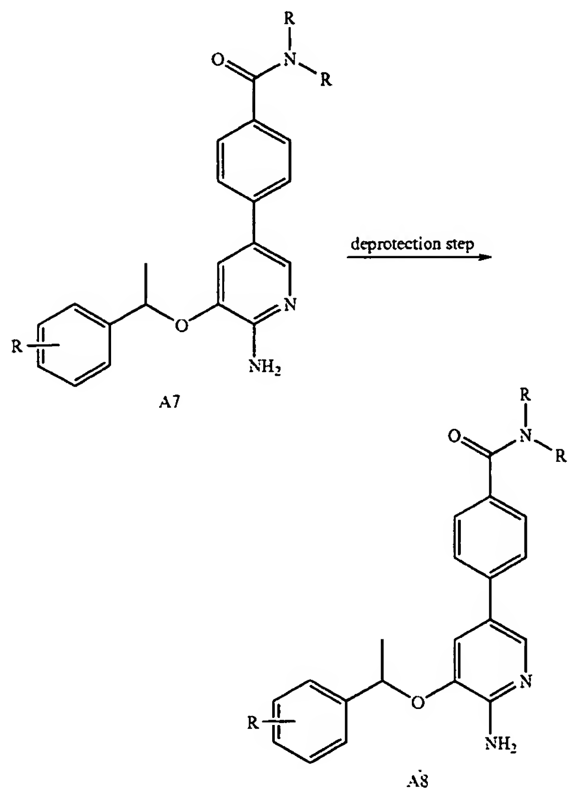


A7

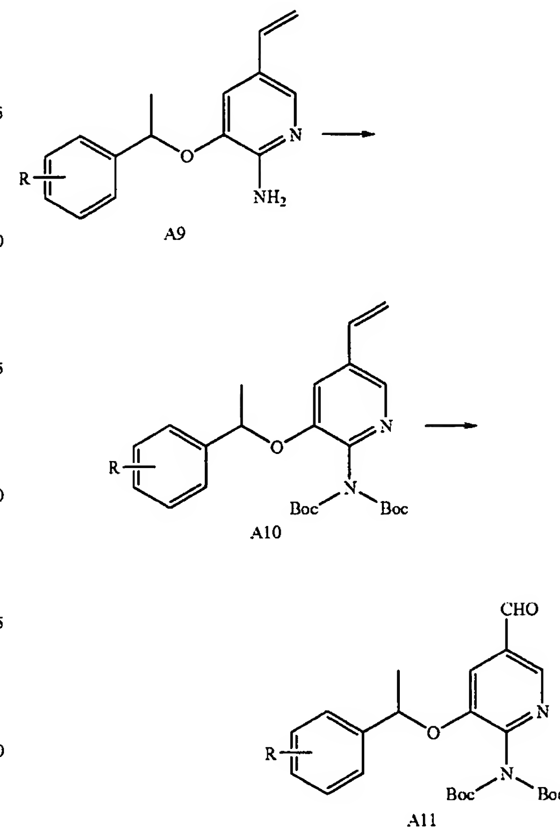
Compound A6 was prepared using general procedure 19. O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium phosphorus pentafloride (HATU) (1.1 molar equivalent), diisopropylethyl amine (5 molar equivalent) and amine (1.3 molar equivalent) were added to a solution of compound A6 (0.17 mmol) in 3 mL of DMF under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 12 hr. Saturated $NaHCO_3$ was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrate was evaporated to give a brown oil residue. The residue was purified by silica gel chromatography (eluting with EtOAc and hexanes) to give desired amide product, compound A7, as a yellow oil.

General Procedure 21:



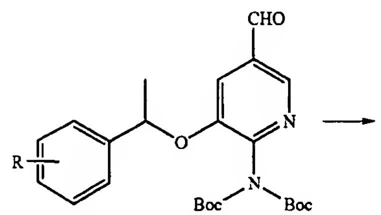
Acid (16 molar equivalent or less) was added to compound A7 (0.13 mmol) at room temperature. The resulting solution was stirred at room temperature or heated to 60° C. for 12 hr. The reaction mixture was evaporated and the residue was purified by silica gel chromatography (eluting with CH_3OH, EtOAc and CH_2Cl_2) to give desired amide product, compound A8, as a yellowish to white solid.

General Procedure 22:

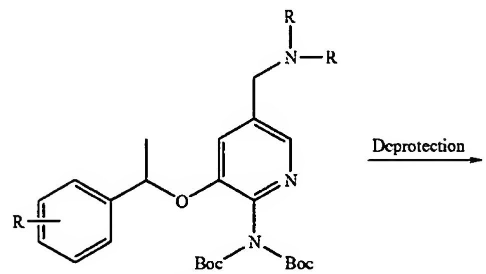


Compound A9 was prepared using general procedure 19. Di-tert-butyl dicarbonate (3 molar equivalent) and 4-(dimethylamino)pyridine (0.14 molar equivalent) were-added to a solution of compound A9 (3 mmol) in 20 mL of DMF. The reaction mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a brown yellow oil residue. The residue was purified by silica gel chromatography (eluting with 25→30% EtOAc in hexanes) to give desired product, compound A10 as a yellowish oil (87.8% yield). Ozone was bubbled through a solution of compound A10 in 50 mL of CH_2Cl_2 at −78° C. and dimethyl sulfide was added to quench the reaction. Saturated sodium chloride was added to the reaction mixture and EtOAc was added to extract the aqueous solution. Combined EtOAc layer was dried over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a yellow oil residue. The residue was purified by silica gel chromatography (eluting with 35→40% EtOAc in hexanes) to give desired product, compound A11 as a yellowish oil (58.4% yield).

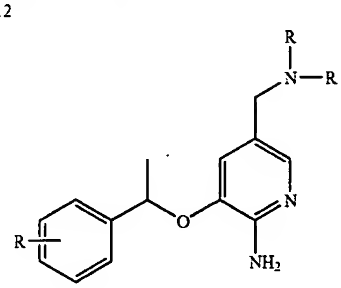
General Procedure 23: Reductive Amination



A11



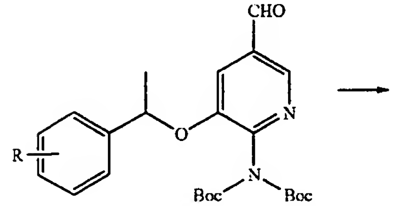
A12



A13

Amine hydrochloride salt (1.2 molar equivalent), sodium acetate (2 molar equivalent to the amine hydrochloride salt) were added to a solution of compound A11 (0.45 mmol) in 4 mL of CH_3OH under a nitrogen atmosphere. Molecular sieve (0.5 g) was added to the reaction mixture and then sodium cyanoborohydride (2 molar equivalent) was added. The resulting mixture was stirred at room temperature for 12 hr under a nitrogen atmosphere. The reaction mixture was filtered through a bed of celite and the filtrate was evaporated and purified by silica gel chromatography (eluting CH_3OH, EtOAc, and CH_2Cl_2) to give desired product, compound A12 as an oil (52.6% yield). Acid (16 molar equivalent or less) was added to compound A12 (0.17 mmol) at room temperature. The resulting solution was stirred at room temperature or heated to 60° C. for 12 hr. The reaction mixture was evaporated and the residue was purified by silica gel chromatography (eluting with CH_3OH, EtOAc and CH_2Cl_2) to give desired product, compound A13.

General Procedure 24:



A11

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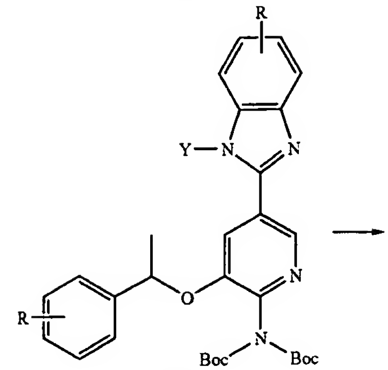
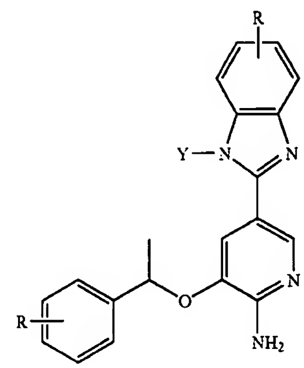


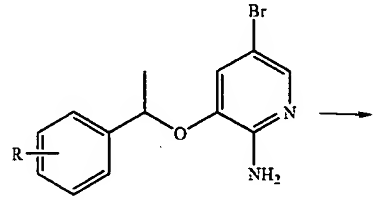
A14



A15

O-phenyldiamines (1.2 molar equivalent) and sodium bisulfite (2:1 molar equivalent) were added to a solution of compound A11 (0.41 mmol) in 5 mL of DMA. The resulting solution was heated to 110° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a brown yellow oil residue. The residue was purified by silica gel chromatography (eluting with EtOAc in hexanes) to give desired product, compound A14. Acid (16 molar equivalent or less) was added to compound A14 (0.16 mmol) at room temperature. The resulting solution was stirred at room temperature or heated to 60° C. for 12 hr. The reaction mixture was evaporated and the residue was purified by silica gel chromatography (eluting with CH_3OH, EtOAc and CH_2Cl_2) to give desired amide product, compound A15.

General Procedure 25:



A3b

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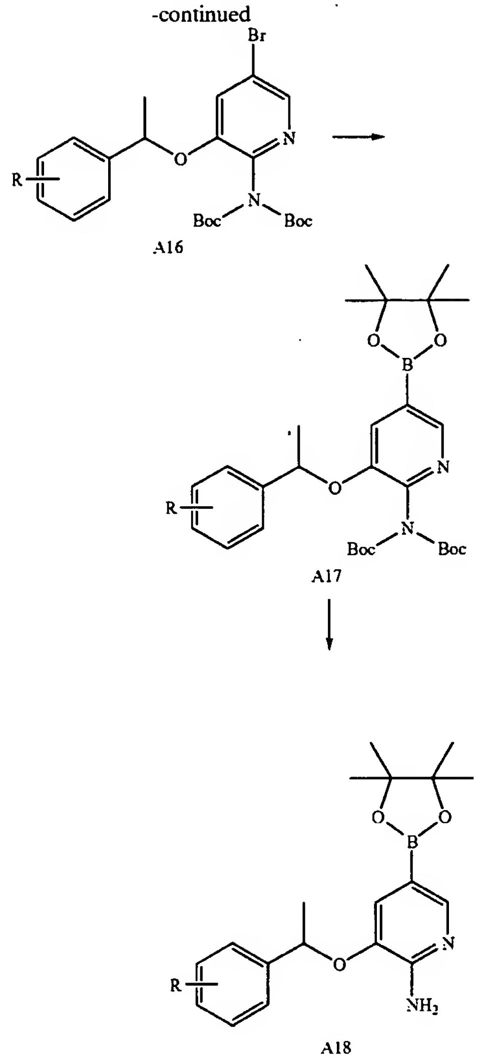


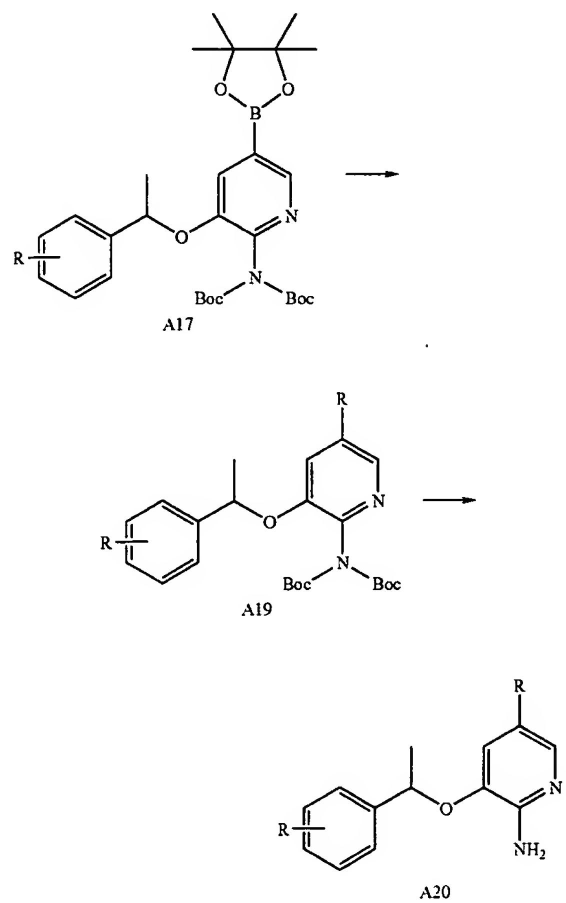
A16, A17, A18

Di-tert-butyl dicarbonate (3 molar equivalent), 4-(dimethylamino)pyridine (0.14 molar equivalent) were added to a solution of compound A3b (2 mmol) in 10 mL of DMF. The reaction mixture was stirred at room temperature for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a brown yellow oil residue (compound a16). The residue was used without further purification.

Bis(pinacolato)diboron (1.2 molar equivalent) and potassium acetate (3.4 molar equivalent) were added to a solution of compound a16 in 4 mL of DMSO. The mixture was perged with nitrogen several times and then dichlorobis (triphenylphsophino) palladium (II) (0.05 molar equivalent) was added. The resulting solution was heated to 80° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a dark brown oil residue. The residue was purified by silica gel chromatography (eluting with 30% EtOAc in hexanes) to give desired product, compound A17 (76% yield). HCl (5

molar equivalent) was added to a solution of compound A17 (0.43 mmol) in 4 mL of CH_2Cl_2. The resulting mixture was heated to 50° C. for 12 hr. Saturated $NaHCO_3$ was added to the reaction mixture to neutralize the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give the desired product (compound A18) as a yellow solid (75% yield).

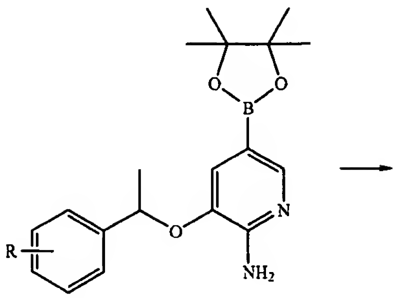
General Procedure 26:



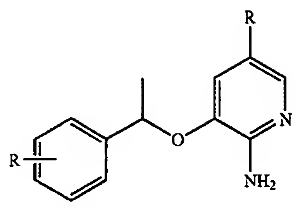
A17, A19, A20

Compound A17 (1.3 molar equivalent) was added to a solution of aryl halide (0.36 mmol) in 3 mL of DME. The mixture was perged with nitrogen several times and then dichlorobis(triphenylphsophino) palladium (II) (0.05 molar equivalent) was added. Sodium carbonate (3 molar equivalent) in 0.8 mL of H_2O was added to the reaction mixture and the resulting solution was heated to 85° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a dark brown oil residue. The residue was purified by silica gel chromatography (eluting with EtOAc in hexanes) to give desired product, compound A19 (74.4% yield). HCl (5 molar equivalent) was added to a solution of compound A19 (0.26 mmol) in 10 mL of isopropyl alcohol. The resulting mixture was heated to 50° C. for 12 hr. The solvent was evaporated to give the desired product, compound A20.

General Procedure 27:



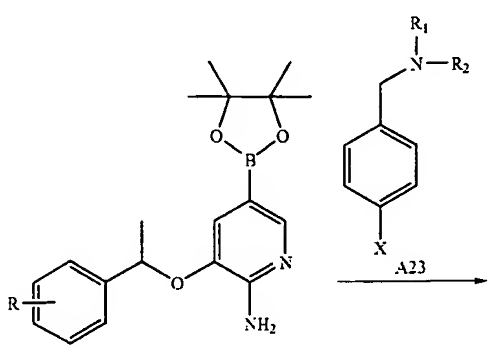
A18



A21

Compound A18 (1.3 molar equivalent) was added to a solution of aryl halide (0.21 mmol) in 3 mL of DME. The mixture was perged with nitrogen several times and then dichlorobis(triphenylphsophino) palladium (II) (0.05 molar equivalent) was added. Sodium carbonate (3 molar equivalent) in 0.6 mL of H_2O was added to the reaction mixture and the resulting solution was heated to 85° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The-Na_2SO_4 was filtered off and the filtrated was evaporated to give a dark brown oil residue. The residue was purified by silica gel chromatography (eluting with CH_3OH, CH_2Cl_2, EtOAc, and hexanes) to give desired product, compound A21.

General Procedure 28:



A17

A23

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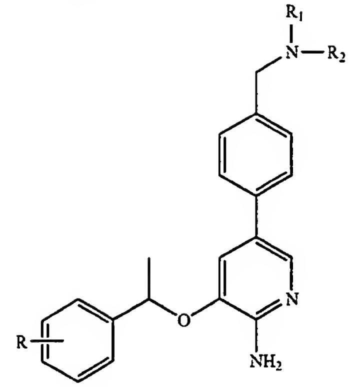
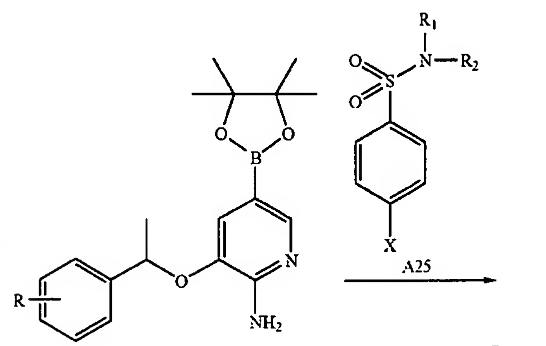


A22

X = I, Br, Cl

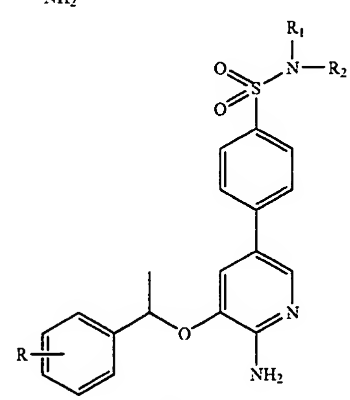
Amine (1.5 molar equivalent) and K_2CO_3 (1.5 molar equivalent) were added to a solution of 4-halobenzyl halide (1.0 molar equivalent) in 2 mL of toluene. The resulting mixture was microwaved using Smithsynthesizer (150° C., 1 hr). Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give the desired product, compound A23. The residue was used in procedure 11 without further purification to synthesize compound A22.

General Procedure 29:



A18

A25

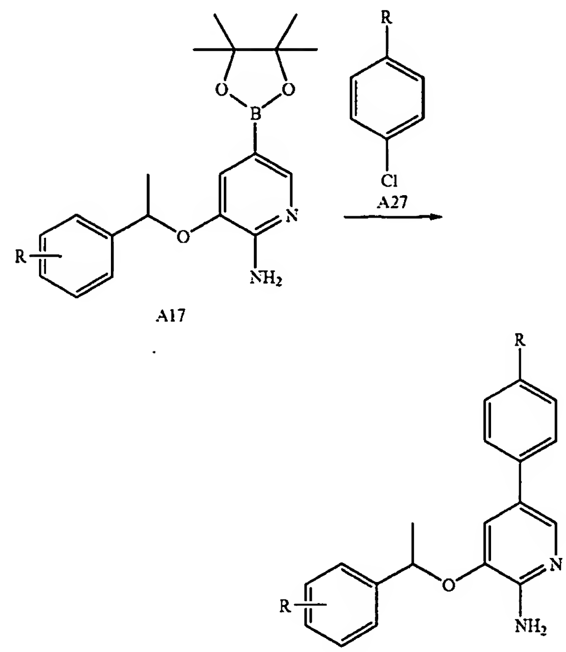


A24

X = I, Br, Cl

Amine (1.2 molar equivalent) and diisopropylamine (5 molar equivalent) were added to a solution of 4-bromobenzenesulfonyl chloride (0.77 mmol) in 5 mL of $CHCl_3$ under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give the desired product, compound A25. The residue was used in procedure 11 without further purification to synthesize compound A24.

General Procedure 30:



A17 A27 A26

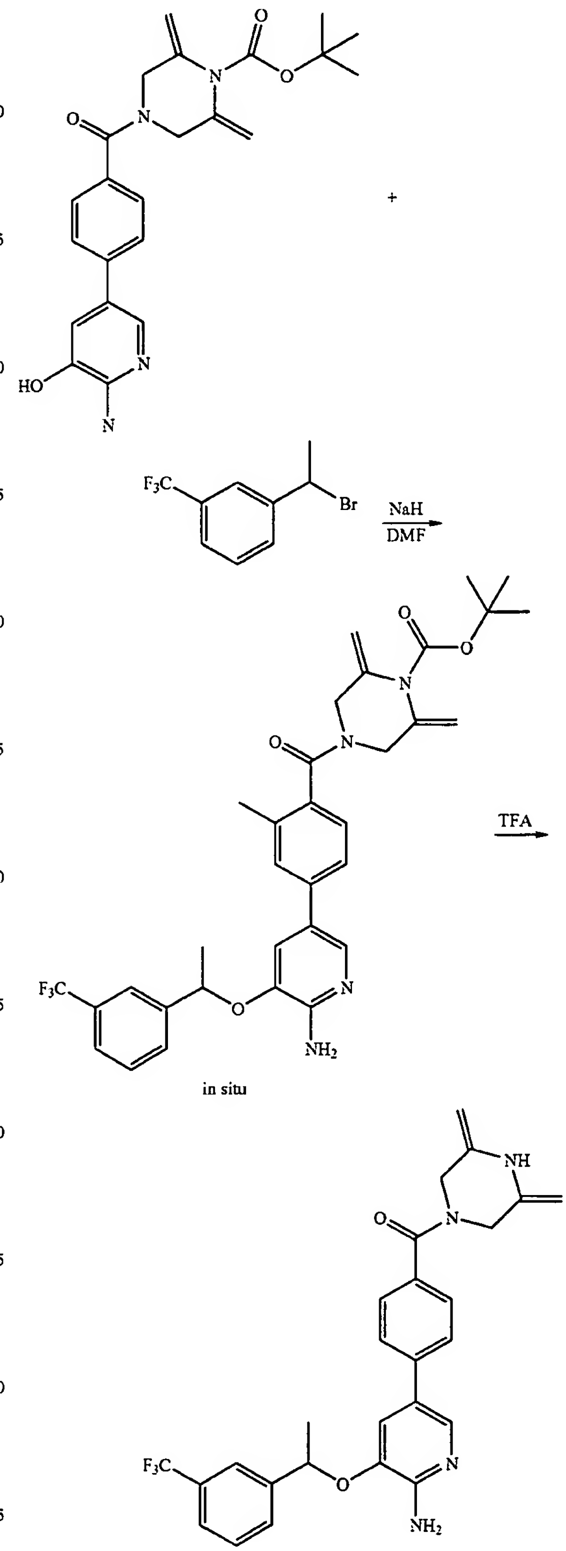
Boronic ester or boronic acid (1.2 molar equivalent) was added to a solution of 1-chloro-4-iodobenzene (0.84 mmol) in 10 mL of ethylene glycol diemthylether (DME) under a nitrogen atmosphere. The mixture was perged with nitrogen several times and then dichlorobis(triphenylphsophino) palladium (II) (0.05 molar equivalent) was added. Sodium carbonate (3 molar equivalent) in 1.8 mL of H_2O was added to the reaction mixture and the resulting solution was heated to 85° C. for 12 hr. Water was added to the reaction mixture to quench the reaction. EtOAc was then added to extract the aqueous solution. Dry EtOAc layer over Na_2SO_4. The Na_2SO_4 was filtered off and the filtrated was evaporated to give a dark brown oil residue. The residue was purified by silica gel chromatography (eluting with CH_3OH, CH_2Cl_2, EtOAc, and hexanes) to give desired product, compound A27. Compound A27 was used in procedure 11 to synthesize compound A26.

General Procedure 31 for Chiral Separation of Racemates:

The racemic sample was purified using preparative supercritical fluid chromatography SFC-MS. The purification conditions were: column-Chiralpak AD-H, 250x21 mm, 5 micron, 100A column (Column #:ADH0CJ-C1003); column temperature 350° C.; mobile phase 35%-methanol (with 0.1% isopropylamine)-modified CO_2; preparative flow rate

52 mL/min; isobaric pressure at 120 bar. The specific chirality of the isomers was not definitively determined.

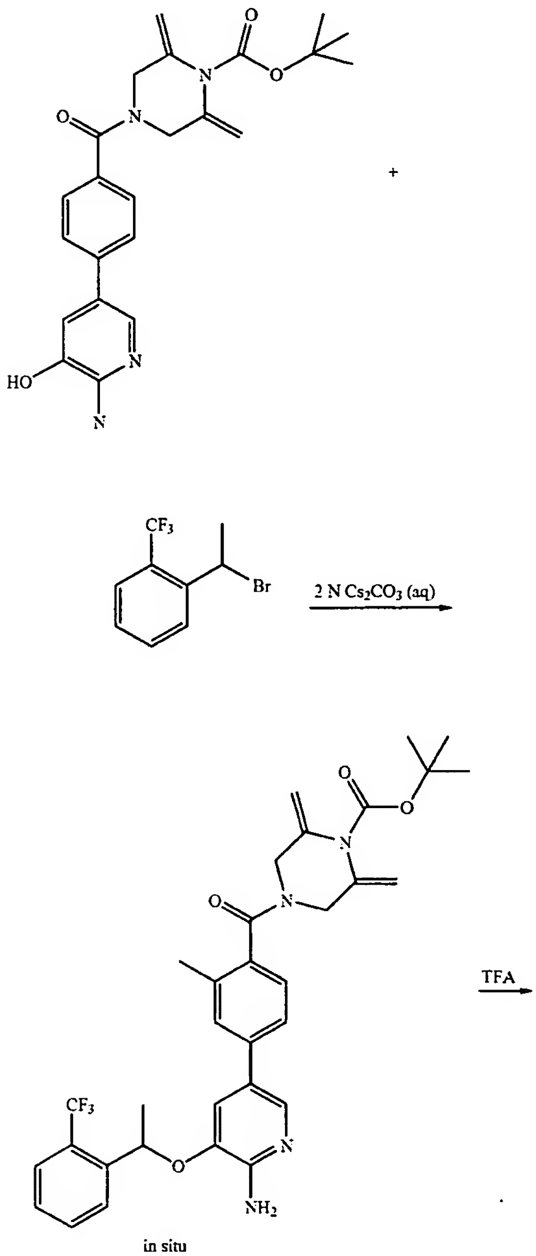
General Procedure 32: using Example I-617



in situ

To a mixture of 4-[4-(6-Amino-5-hydroxy-pyridin-3-yl)-benzoyl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester (100 mg, 0.23 mmol) and 1-(1-bromo-ethyl)-3-trifluoromethyl-benzene (64 mg, 0.25 mmol) in DMF (2 ml) was added NaH (12 mg, 0.47 mmol) at 0° C. The mixture was stirred overnight. LCMS showed that the reaction was completed, DMF and water were removed. TFA (2 mL) was added to the residue and stirred at room temperature for 3 hr. TFA was removed followed by addition of methanol. The residue was purified by prep-HPLC to afford (4-{6-Amino-5-[1-(3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone (30 mg, yield 25.7%).

General Procedure 33: Using Example I-616



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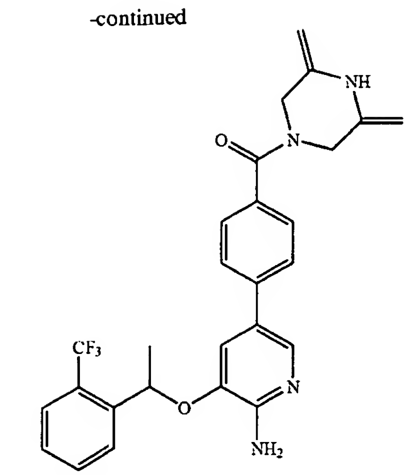
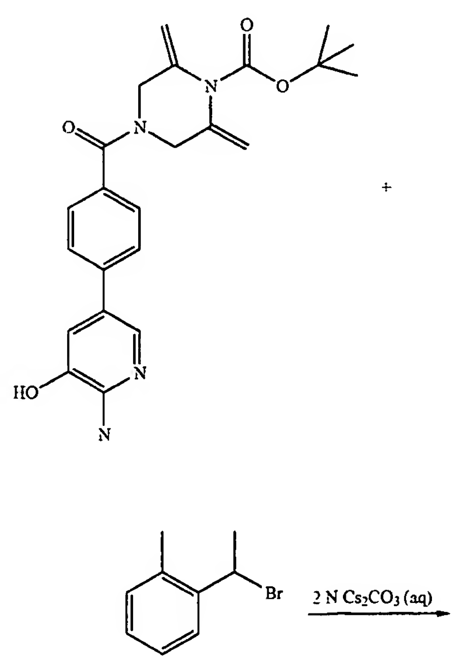


To a mixture of 4-[4-(6-Amino-5-hydroxy-pyridin-3-yl)-benzoyl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) and 1-(1-bromo-ethyl)-2-trifluoromethyl-benzene (32 mg, 0.12 mmol) in DMF (2 ml) was added 2 M Cs_2CO_3 (0.18 mL, 0.35 mmol), followed by water (0.5 mL), the mixture was stirred overnight then heated at 70° C. for 8 hr, LCMS showed that the reaction was completed. The DMF and water were removed. TFA (2 mL was added to the residue and stirred at room temperature for 3 hr. The TFA was removed, followed by addition of methanol. The residue was purified by prep-HPLC to afford (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl)-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone (20 mg, yield 34.2%).

Procedure 34: using Example I-624



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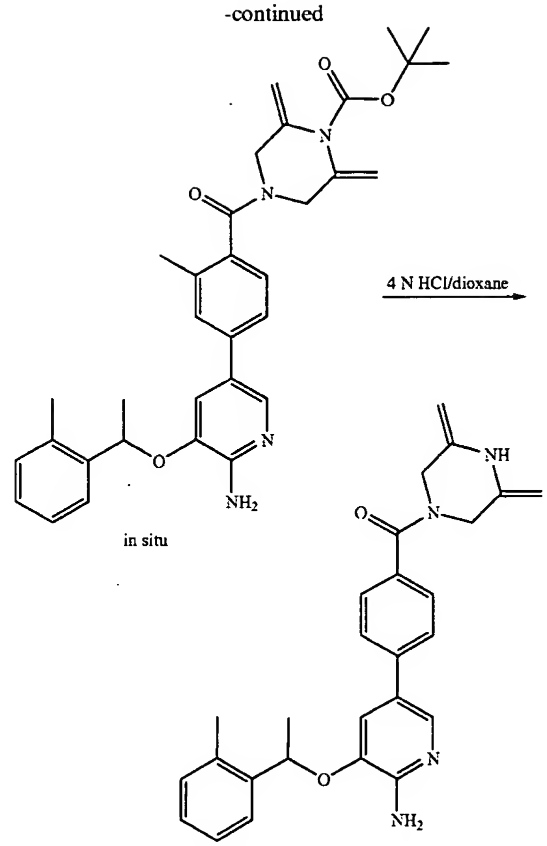
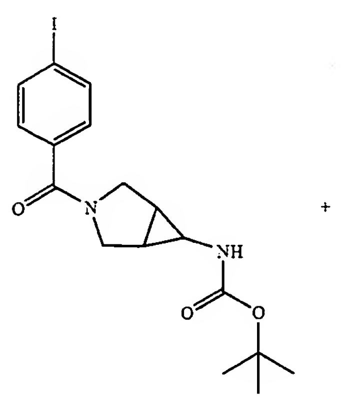


To a mixture of (2R,6S)-4-[4-(6-Amino-5-hydroxy-pyridin-3-yl)-benzoyl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester (100 mg, 0.23 mmol) and 1-bromomethyl-2-methyl-benzene (47 mg, 0.25 mmol) in DMF(2 mL) was added 2 M Cs_2CO_3 (0.35 mL, 0.7 mmol) followed by water (0.5 mL). The mixture was stirred at room temperature overnight. LCMS showed the reaction was completed, DMF was removed, followed by addition of 4 N HCl in dioxane (2 mL) and the reaction was stirred at room temperature for 3 hr. The volatiles were removed followed by addition of methanol. This solution was purified by prep-HPLC to afford {4-[6-Amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone (47 mg, yield 46.6%).

Procedure 35: using Example I-635



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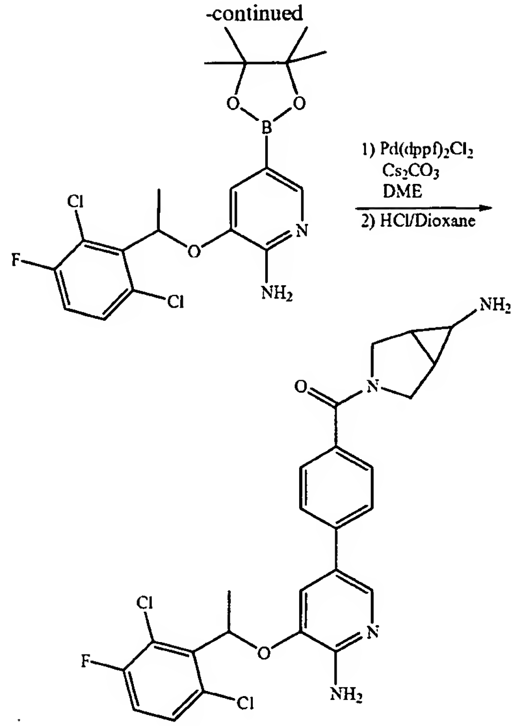
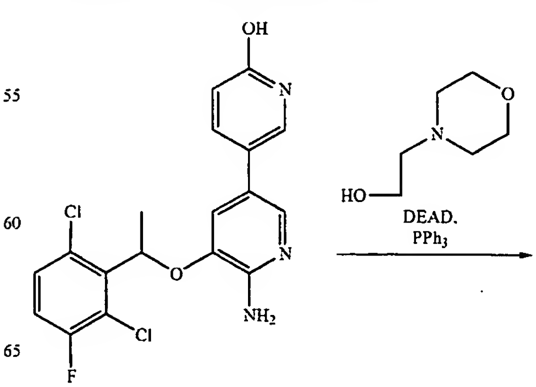


To a mixture of [3-(4-iodo-benzoyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid tert-butyl ester (100 mg, 0.234 mmol) and 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylamine (100 mg, 0.234 mmol) in DME (2 mL) was added $Pd(dppf)_2Cl_2.CH_2Cl_2$ (10 mg, 0.012 mmol) and Cs_2CO_3 (351 mg, 0.702 mmol). The mixture was bubbled with nitrogen for 10 min then microwaved at 150° C. for 30 min. LCMS checked that the reaction was completed. The crude reaction mixture was diluted with ethyl acetate followed by washings with water and brine. The solution was dried over $MgSO_4$. Purification by prep-HPLC afforded a solid. The solid was stirred with 4 N HCl/dioxane (3 mL) for 3 hr at room temperature. Removal of the volatiles led to a residue that was purified by prep-HPLC to afford (6-amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanone (30 mg, yield 26%).

Procedure 36: using Example I-636



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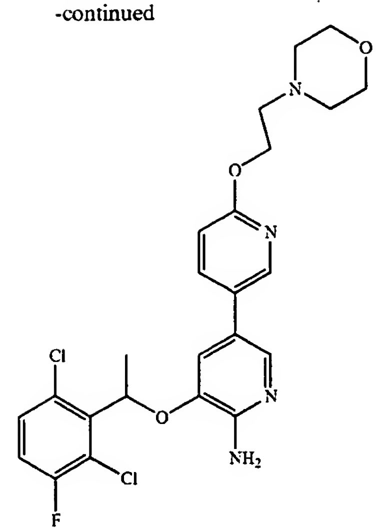
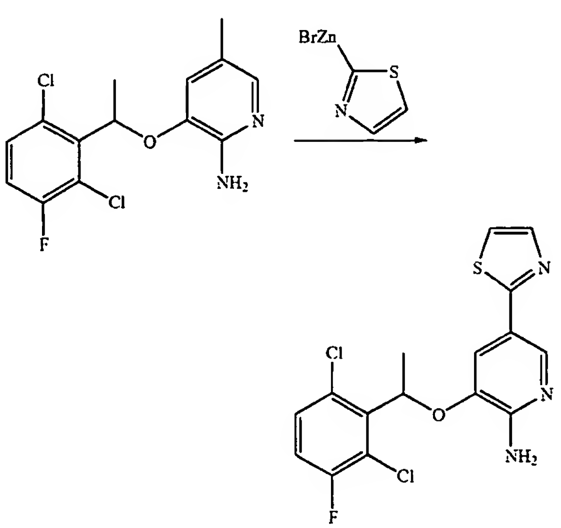


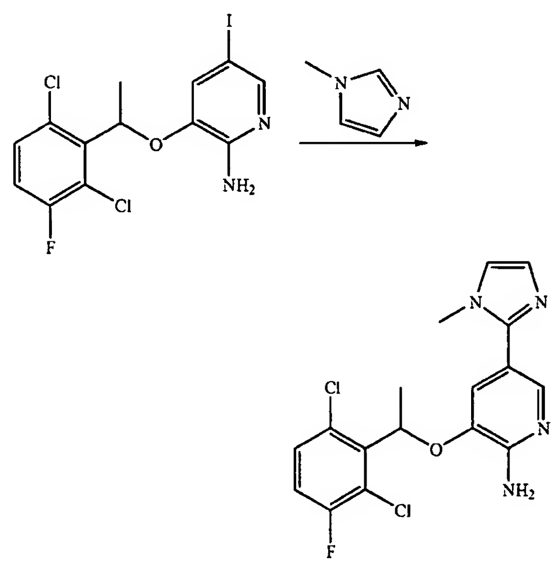
To a mixture of 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ol (78 mg, 0.20 mmol), triphenyphosphine (63 mg, 0.24 mmol) and 2-morpholin-4-yl-ethanol (0.026 mL, 0.22 mmol) was added DEAD (0.034 mL, 0.22 mmol). After stirring overnight more PPh_3 (63 mg, 0.24 mmol) and more DEAD (0.034 mL, 0.22 mmol) were added. After several hours, more alcohol (0.026 mL, 0.22 mmol) was added. After several more hours, more PPh_3 (63 mg, 0.24 mmol) and more DEAD (0.034 mL, 0.22 mmol) were added. After stirring overnight, the mixture was partitioned between dichloromethane and half-saturated brine. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by silica gel chromatography using gradient elution of dichloromethane, methanol to afford 5-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-morpholin-4-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine (53 mg, 53%).

Procedure 37: using Example I-650



3-(2,6-Dichloro-3-fluoro-benzyloxy)-5-thiazol-2-yl-pyridin-2-ylamine: To a microwave tube equipped with a stir bar was added the iodo-pyridyl starting material (300 mg, 0.702 mmol), tetrakis(triphenylphosphine) palladium (0) (40 mg, 5 mol %) and tetrahydrofuran (anhydrous, 6 mL). The vial was capped and purged with nitrogen for 5 minutes. 2-Thiazolylzinc bromide (0.5 M in THF, 1.4 mmol, 2.8 mL) was then added via syringe. The vial was heated to 120° C. in the microwave for 10 minutes. TLC (1:1 ethyl actetate:methylene chloride) showed a large amount of starting material remaining. Additional 2-thiazolylzinc bromide (0.5 M in THF, 500 µL) was added and the vial was heated to 120° C. in the microwave for 20 minutes. TLC (1:1 ethyl actetate: methylene chloride) showed a large amount of starting material still remaining. Additional 2-thiazolylzinc bromide (0.5 M in THF, 500 µL) was added and the vial was heated to 120° C. in the microwave for 60 minutes. TLC (1:1 ethyl actetate:methylene chloride) still showed a large amount of starting material still remaining but also had become very messy. The vial contents were poured into a sat. NH_4Cl solution (10 mL) and this solution extracted with ethyl acetate (2x30 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was loaded onto a 10 g prepacked silica gel column and 1:1 ethyl acetate:methylene chloride used to elute the desired product. (40 mg, 15%).

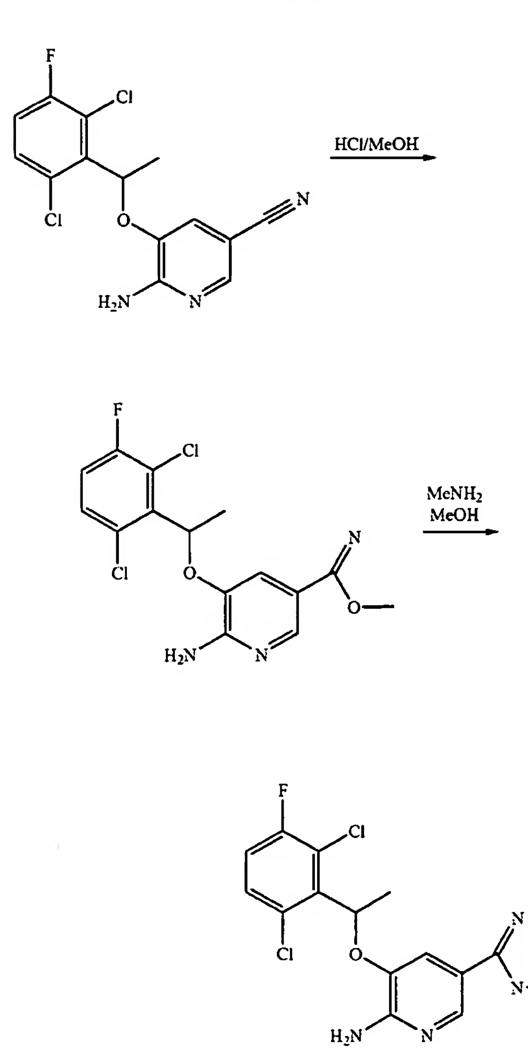
Procedure 38: using Example I-652



3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-methyl-1H-imidazol-2-yl)-pyridin-2-ylamine: N-methyl imidazole (92 mg, 1.1 mmol) was dissolved in tetrahydrofuran (anhydrous, 4 mL) in a 50 mL round bottom flask. The flask was cooled with a dry-ice/acetone bath under nitrogen atmosphere. N-butyl lithium (2.5 M, 562 µL, 1.4 mmol) was added via syringe in 100 µL portions over 5 minutes. The reaction was stirred at −70° C. for 30 minutes. Solid zinc chloride (anhydrous, 383 mg, 2.8 mmol) was added and the reaction stirred for 15 minutes. The ice bath was then removed and the reaction allowed to warm to room temperature. Once all of the zinc chloride was in solution-and the reaction at room temperature, iodo scaffold (400 mg, 0.936 mmol) was added in tetrahydrofuran (anhydrous, 4 mL), followed by tetrakis(triphenylphosphine) palladium

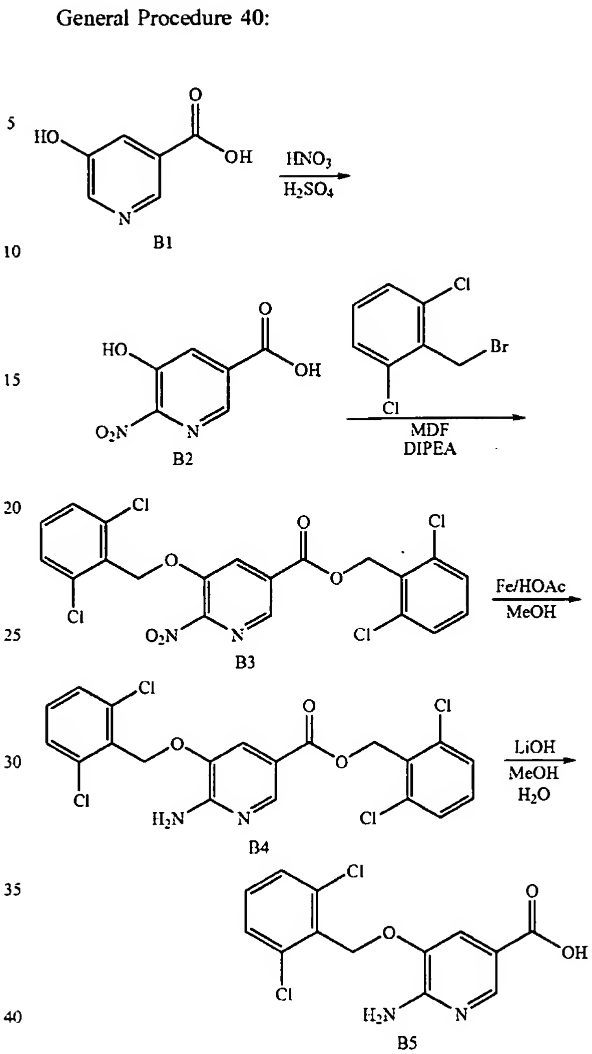
(0) (108 mg, 10 mol %) and the reaction heated to reflux. The reaction was monitored by LC/MS until all of the starting iodo scaffold was consumed. The reaction was allowed to cool and then diluted with a sat. NH_4Cl solution (20 mL). This solution was extracted with ethyl acetate (2×50 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was loaded onto a 10 g prepacked silica gel column and 10% methanol:ethyl acetate was used to elute the desired product (25 mg, 7%).

General Procedure 39: using Example I-657



To 6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile (400 mg, 1.23 mmol) in 70 mL dry methanol at 0° C. was bubbled HCl gas for 3 minutes. Stirred overnight at 3° C. Removed volatiles and washed the solids with diethyl ether to yield quanitatively the imidate. To 200 mg of the imidate in 4 mL methanol at 0° C. was added 2N methylamine in THF (837 μL). Let stir at 0° C. for about 1 hr then let warm to rt overnight. The volatiles were removed and the residue was chromatographed with 10–20% methanol/dichloromethane to yield 70 mg of product.

General Procedure 40:



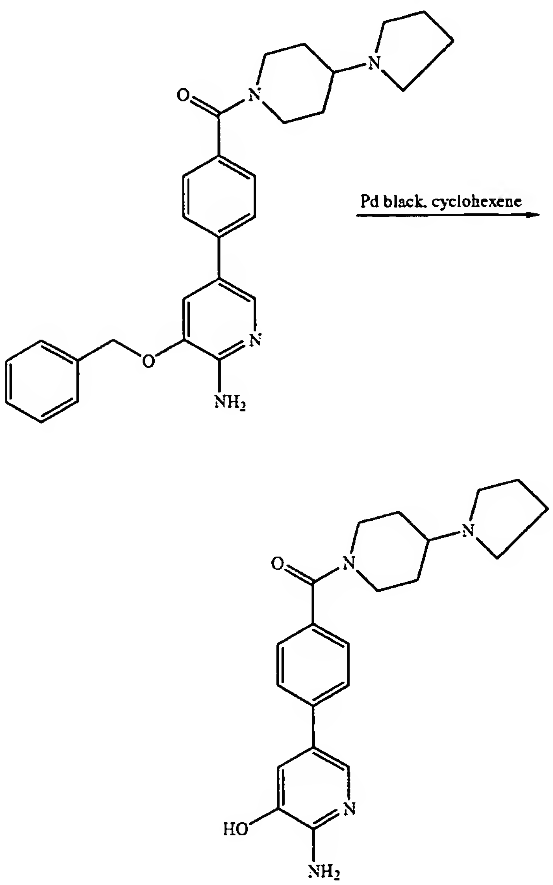
1. 6-Nitro-5-hydroxynicotinic acid (B2): To a solution of 5-hydroxynicotinic acid (B_1) (7.0 g, 50 mmol) in concentrated H_2SO_4 was added 9 mL of fuming HNO_3 (90%) (9 mL). The reaction mixture was stirred at 55–60° C. in a sealed tube for four days. The mixture was then poured into ice and the pH was adjusted to 3 with 50% NaOH. $MgSO_4$ was added to saturate the aqueous mixture, which was then extracted with isopropyl alcohol (4×45 mL). After the removal of isopropyl alcohol under reduced pressure, 5.93 9 (64% yield) of B2 was obtained as a yellow solid. MS (APCI), $(M+H)^+185$. ^{1}HNMR (DMSO-d6) δ 8.01 (d, 1H, Ar—H), 8.41(d, 1H, Ar—H).

2. 2,6-Dichlorobenzyl-6-nitro-5-[(2,6-dichlorobenzyl)oxy]nicotinate (B3): 6-nitro-5-hydroxynicotinic acid (B2) (3.4 g, 18.5 mmol), 2,6-dichlorobenzyl bromide (8.88–9, 37 mmol), DIPEA (5.5 g, 42.5 mmol) were dissolved in DMF (25 mL) in a 250 mL round bottomed flask and the reaction was stirred at room temperature for 4.5 hr and then concentrated under reduced pressure. The resulting mixture was poured into ice and the filtered. The solid collected was dried under reduced pressure to give 4.25 g (46% yield) of B3 MS (APCI) (M+H)+503. ^{1}HNMR (DMSO-d6) δ 5.47 (s, 2H,

$ArCH_2O$), 5.71 (s, 2H, $ArCH_2O$), 7.24–7.43 (m, 6H, Ar—H), 8.26(d, 1H, Ar—H), 8.66(d, 1H, Ar—H).

3. 2,6-Dichlorobenzyl-6-amino-5-[(2,6-dichlorobenzyl)oxy]nicotinate (B4): A mixture of 2,6-dichlorobenzyl-6-nitro-5-[(2,6-dichlorobenzyl)oxy]nicotinate (B3) (5.5 g, 10.96 mmol), iron powder (0.92 g, 16.43 mmol), glacial acetic acid (20 mL) and methanol (17 mL) was stirred at 85° C. for three hr. The reaction mixture was concentrated to near dryness, and ammonium hydroxide (30%) was added to neutralize the mixture. Minimum amount of DMF was added to dissolve the reaction mixture, which was purified by flash column chromatograph (eluent: EtOAc-EtOH, 9:1) to give 4.5 g (87%) of B4 as a pale yellow solid. MS (APCI) $(M+H)^+$473.

4. 6-Amino-5-[(2,6-dichlorobenzyl)oxy]nicotinic acid (B5): A mixture of 2,6-dichlorobenzyl-6-amino-5-[(2,6-dichlorobenzyl)oxy]nicotinate (B4) (3.5 g, 7.4 mmol), lithium hydroxide (0.41 g, 17 mmol), water (22 mL) and methanol (30 mL) was stirred and reflux at 85° C. for 5 hr. The mixture was concentrated to dryness under reduced pressure. The resulting residue was dissolved in water, extracted with a mixture of Et_2O/hexane (1:1, 4×25 mL), neutralized with 1N HCl to form white precipitation, which was filtered and dried under reduced pressure to provide 1.83 grams (79%) of B5 as a white solid. MS (APCI) (M+H)+313. ^{1}HNMR (DMSO-d6) 3 5.26 (s, 2H, $ArCH_2O$), 6.37 (s, 2H, NH_2), 7.43–7.48 (t, 1H, Ar—H), 7.54 (s, 2H, Ar—H), 7.56 (s, 1H, Ar—H), 8.18 (s, 1H, Ar—H).



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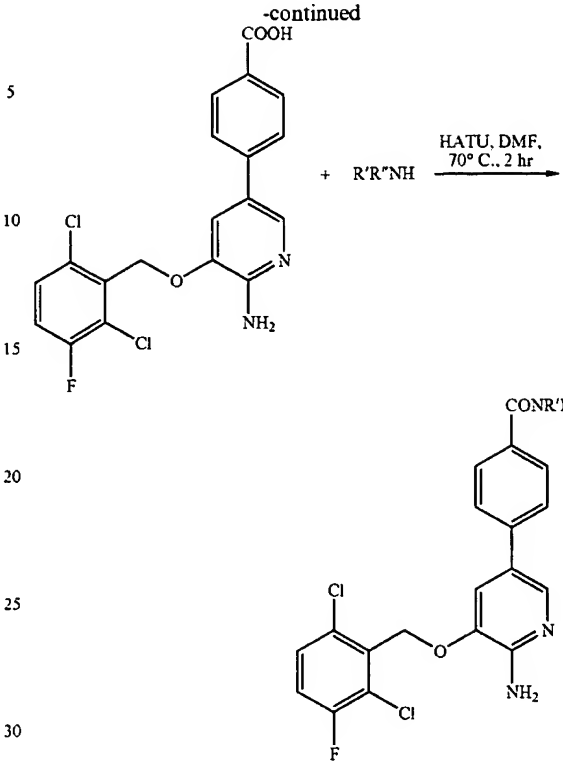
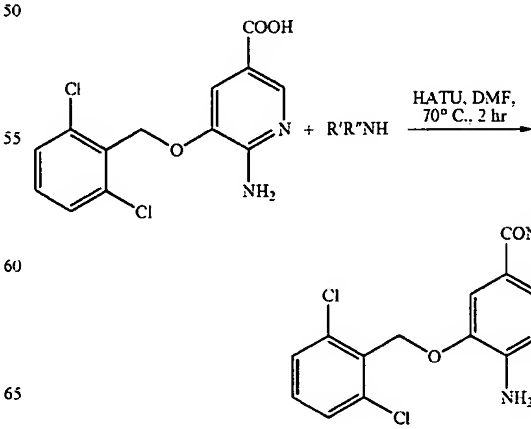


To an array of 400 μL of 0.2 M solution of different amines in DMF in a 96-well plate was added 400 μL (0.2 M in DMF) of 4-[6-amino-5-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid, 80 μL of triethylamine (1 M in DMF) and 160 μL of HATU (0.5 M in DMF) and the reactions were stirred at 70° C. for 2 hr. The solvent was removed using the SpeedVac apparatus and the crude reaction mixtures were redissolved in DMSO and transferred using a liquid handler to a 1 mL 96-well plate to give a final theoretical concentration of ~10 mM. The reactions were analyzed and positive product identification was made using LC/MS. The mother stock solution was diluted to 50 nM and assayed for percent inhibition of c-MET at 50 nM.

General Procedure 41:



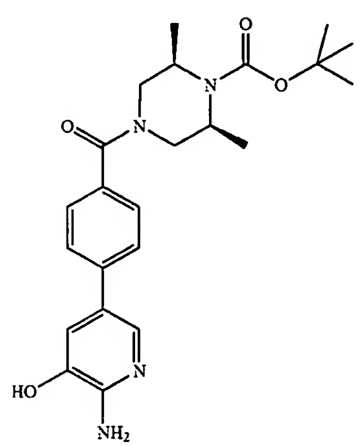
To an array of 400 mL of 0.2 M solution of different amines in DMF in a 96-well plate was added 400 μL (0.2 M in DMF) of 6-Amino-5-[(2,6-dichlorobenzyl)oxy]nicotinic acid, 80 μL of triethylamine (1 M in DMF) and 160 μL of HATU (0.5 M in DMF) and the reactions were stirred at 70° C. for 2 hr. The solvent was removed using the SpeedVac apparatus and the crude reaction mixtures were redissolved in DMSO and transferred using a liquid handler to a 1 mL 96-well plate to give a final theoretical concentration of ~10 mM. The reactions were analyzed and positive product identification was made using LC/MS. The mother stock solution was diluted to 1 μM and assayed

General Procedure 42:

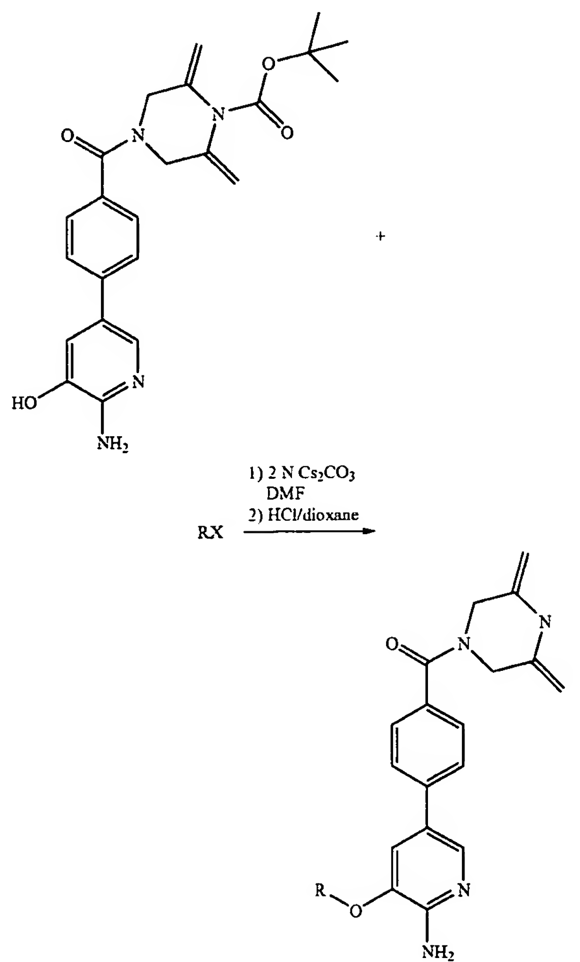
[4-(6-Amino-5-hydroxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone: To a solution of [4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone (3.67 g, 8.1 mmol) in 100 ml ethanol was added 25 ml cyclohexane and 367 mg palladium black. Reluxed overnight. The solution was filtered and the volatiles were removed. To the residue was added 60 mL of MeOH, 20 mL cyclohexene and 350 mg Pd black. Refluxed-overnight. Filtered and removed volatiles, resuspended in methanol, added 350 mg Pd black and hydrogenated at 1 atm overnight (pressure reactors all busy). Filtered and isolated 3.0 grams of a solid foam. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 7.82 (d, J=2.02 Hz, 1H) 7.58 (d, J=8.34 Hz, 2H) 7.41 (d, J=8.34 Hz, 2H) 7.12 (d, J=2.02 Hz, 1H) 5.74 (s, 2H) 3.33 (s, 5H) 3.08 (s, 2H) 1.95 (m, 8H) 1.49 (s, 2H). LC/MS (APCI) 367 m/e (M+1).

To an array of 10×75 mm test tubes were added [4-(6-Amino-5-hydroxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone (0.2 M in DMF, 80 μmol, 1.0 eq.), Cs_2CO_3 (2 M, 160 μmol, 2.0 equiv) and different alkyl halides (0.2 M in DMF, 88 μmol, 1.1 eq.). The reactions were stirred at room temperature overnight. In order to separate the inorganic salts, the resulting suspension was evaporated and DMF (625 μL) was added. After agitation, the mixture was centrifuged to settle the solid residue, and the supernatant was transferred to a new 10×75 mm test tube. The reactions were analyzed and positive product identification was made using LC/MS. The mother stock solution was diluted to 1 μM and assayed.

General Procedure 43:



(2R,6S)-4-[4-(6-Amino-5-hydroxy-pyridin-3-yl)-benzoyl]-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester: See general procedure IG. Yield 83.5%. ^{1}H NMR (400 MHz, DMSO-D6) δppm 7.81 (d, J=2.27 Hz, 1H) 7.57 (d, J=8.34 Hz, 2H) 7.41 (d, J=8.34 Hz, 2H) 7.12 (d, J=2.02 Hz, 1H) 5.70



(s, 2H) 4.07 (s, 2H) 3.31 (s, 3H) 1.39 (s, 10H) 1.03–1.14 (m, 7H)

To an array of 10×75 mm test tubes were added [4-(6-Amino-5-hydroxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone (0.2 M in DMF, 80 μmol, 1.0 eq.), Cs_2CO_3 (2 M, 160 μmol, 2.0 equiv) and different alkyl halides (0.2 M in DMF, 88 μmol, 1.1 eq.). The reactions were stirred at room temperature overnight. In order to separate the inorganic salts, the resulting suspension was evaporated and DMF (625 μL) was added. After stirring, the mixture was centrifuged to settle the solid residue, and the supernatant was transferred to a new 10×75 mm test tube. The solid residues were extracted with more DMF (400 μL) and the extracts were combined with the first organic layer. The DMF was evaporated, and HCl (4 M in dioxane, 2.5 mmol, 31 eq.) was added to the reaction mixture in the receiving test tube. The reaction mixture was stirred at room temperature for 3 hr. The reactions were analyzed and positive product identification was made using LC/MS. The mother stock solution was diluted to 1 μM and assayed.

Example I(a)

1. To a stirred solution of Cs_2CO_3 (11.63 g, 35.69 mmol) in DMF (180 mL) under a N_2 atmosphere containing 3-hydroxy-4-nitro-pyridine (5 g, 35.69 mmol) was added 2,6-dichlorobenzyl bromide (8.56 g, 35.69 mmol). The mixture was stirred for 6 h at ambient temperature. The reaction was then diluted with EtOAc (400 mL) and partitioned with H_2O (100 mL). The aqueous layer was extracted with EtOAc (2×50 mL). The organic layers were then combined and washed with H_2O (2×50 mL) and brine (1×50 mL). The organics were dried over Na_2SO_4, filtered and concentrated to dryness under vacuum to yield 3-(2,6-dichloro-benzyloxy)-2-nitro-pyridine (10.5 g, 98.4%) as a white solid.

2. To a stirred mixture of AcOH (650 mL) and EtOH (500 mL) was suspended 3-(2,6-dichloro-benzyloxy)-2-nitro-pyridine (37.4 g, 0.11 mol) and iron chips (69.4 g, 0.11 mol). The reaction was heated slowly to reflux and allowed to stir for 1 hr. The reaction was cooled to room temperature then filtered through a pad of celite. The resulting filtrate was neutralized with conc. NH_4OH (600 mL) and then extracted with EtOAc (3×500 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×100 mL), H_2O (2×100 mL) and brine (1×100 mL) then dried (Na_2SO_4), filtered and concentrated to dryness under vacuum to yield 3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (32.4 g, 0.11 mol, 99%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (m, 3H), 7.46 (dd, 2H), 7.36 (d, 1H), 6.62 (dd, 1H), 6.18 (br s, 2H, NH_2), 5.24 (s, 2H); MS m/z 270 [M+1].

3. A stirring solution of 3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (32.4 g, 0.11 mol) in acetonitrile was cooled to 0° C. using an ice bath. To this solution was added N-bromosuccinimide (19.5 g, 0.11 mol) portionwise. The reaction was stirred at 0° C. for 15 min. The reaction was concentrated to dryness under vacuum. The resulting dark oil was dissolved in EtOAc (500 mL) and partitioned with H_2O (250 mL). The organic was then washed with sat'd $NaHCO_3$ (2×200 mL) and brine (1×200 mL). Activated charcoal was added to the organic layer and warmed to reflux. The solution was then cooled to room temperature and filtered through a pad of celite. The organic was then concentrated to dryness under vacuum to one third the original volume. The solids were then filtered off to yield 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (22.0 g, 0.07 mol, 64%) as a tan solid. The remaining filtrate was concentrated under vacuum to yield crude 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (12.1 g, 0.04 mol, 35%) as a brown solid.

Example I(b)

3-Benzyloxy-5-bromo-pyridin-2-ylamine was prepared following procedure 1 from 3-benzyloxy-pyridin-2-ylamine as a tan solid in 65% yield.

Example I(c)

5-Bromo-3-(2,6-difluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2,6-difluoro-benzyloxy)-2-nitro-pyridine was prepared in 99% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (m, 2H), 7.79 (dd, 1H), 7.52 (m, 1H), 7.16 (m, 2H), 5.37 (s, 2H); MS m/z 266 [M+]. 3(2,6-Difluoro-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 2H), 7.64 (dd, 1H), 7.57 (m, 2H), 6.84 (dd, 1H), 5.24 (s, 2H); MS m/z 237 [M+1]. 5-Bromo-3-(2,6-difluoro-benzyloxy)-pyridin-2-ylamine was prepared in 91% yield.

Example I(d)

5-Bromo-3-(2-bromo-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-bromo-benzyloxy)-2-nitro-pyridine intermediate was prepared in 99% yield as a white solid. 3-(2-bromo-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield as a solid. 5-Bromo-3-(2-bromo-benzyloxy)-pyridin-2-ylamine was obtained in 37% yield as a tan solid.

Example I(e)

5-Bromo-3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-chloro-6-fluoro-benzyloxy)-2-nitro-pyridine was prepared in 90% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (m, 2H), 7.80 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 5.39 (s, 2H). 3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine was prepared in 88% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70–7.15 (m, 5H), 6.45 (m, 1H), 5.45 (br s, 2H), 5.06 (s, 2H). 5-Bromo-3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine was prepared in 81% yield.

Example I(f)

5-Bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-chloro-4-fluoro-benzyloxy)-2-nitro-pyridine was prepared in 91% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (m, 2H), 7.75 (m, 1H), 7.63 (m, 1H), 7.55 (m, 1H), 7.25 (m, 1H), 5.45 (s, 2H). 3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (m, 2H), 7.47 (m, 1H), 7.20 (m, 1H), 7.08 (m, 1H), 6.45 (m, 1H), 5.62 (br s, 2H), 5.08 (s, 2H). 5-Bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine was prepared in 63% yield.

Example I(g)

5-Bromo-3-(2,4-dichloro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2,4-Dichloro-benzyloxy)-2-nitro-pyridine was prepared in 96% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05–7.50 (m, 6H), 5.39 (s, 2H); MS (m/z) 299 (M+1). 3-(2,4-Dichloro-benzyloxy)-pyridin-2-ylamine was prepared in 98% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65–6.25 (m, 6H), 5.85 (br s, 2H), 5.06 (s, 2H). 5-Bromo-3-(2,4-dichloro-benzyloxy)-pyridin-2-ylamine was prepared in 65% yield.

Example I(h)

2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile was prepared following procedure 1. 2-(2-Nitro-pyridin-3-yloxymethyl)-benzonitrile was prepared in 91% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15–7.55 (m, 1H), 5.50 (s, 2H). 2-(2-Amino-pyridin-3-yloxymethyl)-benzonitrile was prepared in 86% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95–6.45 (m, 7H), 5.65 (br s, 2H), 5.20 (s, 2H). 2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile was prepared in 77% yield.

Example I(i)

5-Bromo-3-(2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-trifluoromethyl-benzyloxy)-2-nitro-pyridine was prepared in 92% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05–7.58 (m, 7H), 5.45 (s, 2H). 3-(2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine was prepared in 80% yield as a tan solid. 5-Bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine was prepared in 43% yield as a solid.

Example I(j)

5-Bromo-3-(4-tert-butyl-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(4-tert-butyl-benzyloxy)-2-nitro-pyridine was prepared in 80% yield as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10–7.30 (m, 7H), 5.30 (s, 2H), 1.25 (s, 9H). 3-(4-tert-Butyl-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45–6.25 (m, 7H), 5.58 (br s, 2H), 5.05 (s, 2H), 1.25 (s, 9H). 5-Bromo-3-(4-tert-butyl-benzyloxy)-pyridin-2-ylamine was prepared in 55% yield as a solid.

Example I(k)

5-Bromo-3-(2-chloro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-Chloro-benzyloxy)-2-nitro-pyridine was prepared in 89% yield as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10–7.40 (m, 7H), 5.40 (s, 2H). 3-(2-Chloro-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65–6.45 (m, 7H), 5.62 (br s, 2H), 5.10 (s, 2H). 5-Bromo-3-(2-chloro-benzyloxy)-pyridin-2-ylamine was prepared in 22% yield as a solid.

Example I(l)

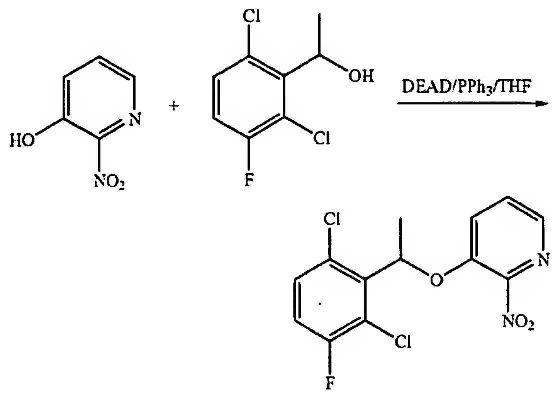
5-Bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. 3-(2-chloro-3,6-difluoro-benzyloxy)-2-nitro-pyridine intermediate was prepared in 99% yield as an off white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ5.31 (s, 2H), 7.02–7.09 (dt, 1H, J, 4, 8), 7.17–7.23 (dt, 1H, J, 4.5, 8.4), 7.54–7.58 (dd. 1H, J, 4.5, 8.4), 7.71–7.68 (dd, 1H, J, 1.21, 8.4), 8.14–8.16 (dd, 1H, J, 1.23, 4.5). 3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine was prepared in 100% yield as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.6–4.8 (brs, 2H), 5.2 (s, 2H), 7.0–7.08 (dt, 1H, J, 4.1, 9.0), 7.09–7.12 (dd, 1H, J, 1.0, 7.8), 7.15–7.22 (dt, 1H, J, 4.8, 8.0), 7.69–7.71 (dd, 1H, J, 1.2, 5.1). 5-Bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine was obtained in 64% yield as a tan solid.

Example I(m)

5-Bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1 starting from 3-hydroxy-4-nitro-pyridine and 1-bromomethyl-3-fluoro-2-trifluoromethyl-benzene.

Example I(n)

1. 2,6-Dichloro-3-fluoroacetophenone (15 g, 0.072 mol) was stirred in THF (150 mL, 0.5 M) at 0° C. using an ice bath for 10 min. Lithium aluminum hydride (2.75 g, 0.072 mol) was slowly added. The reaction was stirred at ambient temperature for 3 hr. The reaction was cooled in ice bath, and water (3 mL) was added drop wisely followed by adding 15% NaOH (3 mL) slowly. The mixture was stirred at ambient temperature for 30 min. 15% NaOH (9 mL), $MgSO_4$ were added and the mixture filtered to remove solids. The solids were washed with THF (50 mL) and the filtrate was concentrated to give 1-(2,6-Dichloro-3-fluoro-phenyl)-ethanol (14.8 gm, 95% yield) as a yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.45 (d, 3H), 5.42 (m, 2H), 7.32 (m, 1H), 7.42 (m, 1H).



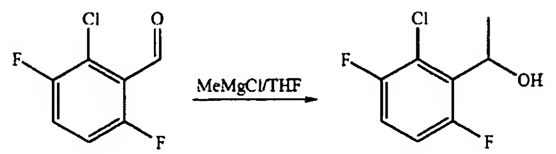
2. To a stirred solution of triphenyl phosphine (8.2 g, 0.03 mol) and DEAD (13.65 mL of a 40% solution in toluene) in THF (200 mL) at 0° C. was added a solution of 1-(2,6-dichloro-3-fluoro-phenyl)-ethanol (4.55 g, 0.021 mol) and 3-hydroxy-nitropyridine (3.35 g, 0.023 mol) in THF (200 mL). The resulting bright orange solution was stirred under a nitrogen atmosphere at ambient temperature for 4 hours at which point all starting materials had been consumed. The solvent was removed, and the crude material was dry loaded onto silica gel, and eluted with ethyl acetate-hexanes (20:80) to yield 3-(2,6-dichloro-3-fluoro-benzyloxy)-2-nitro-pyridine (6.21 g, 0.021 mol, 98%) as a pink solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.8–1.85 (d, 3H), 6.0–6.15 (q, 1H), 7.0–7.1 (t, 1H), 7.2–7.21 (d, 1H), 7.25–7.5 (m, 2H), 8.0–8.05 (d, 1H).

3. 3-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. To a stirred mixture of AcOH (650 mL) and EtOH (500 mL) was suspended 3-(2,6-dichloro-3-fluoro-benzyloxy)-2-nitro-pyridine (9.43 g, 0.028 mol) and iron chips (15.7 g, 0.28 mol). The reaction was heated slowly to reflux and allowed to stir for 1 hr. The reaction was cooled to room temperature then diethyl ether (500 mL) and water (500 mL) was added. The solution was carefully neutralized by the addition of sodium carbonate. The combined organic extracts were washed with sat'd $NaHCO_3$ (2×100 mL), H_2O (2×100 mL) and brine (1×100 mL) then dried (Na_2SO_4), filtered and concentrated to dryness under vacuum to yield 3-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-2-ylamine (9.04 g, 0.027 mol, 99%) as a light pink solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.8–1.85 (d, 3H), 4.9–5.2 (brs; 2H), 6.7–6.84 (q, 1H), 7.0–7.1 (m, 1H), 7.2–7.3 (m, 1H), 7.6–7.7 (m, 1H).

4. 5-bromo-3-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-2-ylamine was prepared following procedure 1. A stirring solution of 3-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-2-ylamine (9.07 g, 0.03 mol) in acetonitrile was cooled to 0° C. using an ice bath. To this solution was added NBS (5.33 g, 0.03 mol) portionwise. The reaction was stirred at 0° C. for 15 min. The reaction was concentrated to dryness under vacuum. The resulting dark oil was dissolved in EtOAc (500 mL), and purified via silica gel chromatography. The sol-

vents were then removed in vacuo to yield 5-bromo-3-(2,6-dichloro-3-fluoro-benzyloxy)-pyridin-2-ylamine (5.8 g, 0.015 mol, 51%) as a white crystaline solid.

Example I(o)



1. 2-Chloro-3,6-difluorobenzaldehyde (1.0 molar equivalent) was dissolved in THF (0.2 M) and stirred at 0° C. for 5 min. The corresponding methylmagnesium chloride solution (1.1 molar equivalent) was added. The reaction was warmed up gradually to ambient temperature and stirred for 2 hr. Methanol, and 1 N HCl was added to the mixture and diluted with ethyl acetate. The mixture was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give 1-(2-chloro-3,6-difluoro-phenyl)-ethanol as oil. ^1H NMR (400 MHz, DMSO-d_6) δ 1.42 (d, 3H), 5.21 (m, 1H), 5.42 (m, 1H), 7.09 (m, 1H), 7.18 (m, 1H).

2. 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine was prepared following the same procedure as Example I(n) starting from 1-(2-chloro-3,6-difluoro-phenyl)-ethanol and 3-hydroxy-nitropyridine.

Example II(a)

To an ice cooled solution of (2,6-dichloro-phenyl)-methanol (5 g, 28.2 mmol) in anhydrous tetrahydrofuran (200 mL) was added sodium hydride (1.13 g, 28.2 mmol, 60% disp.) slowly under nitrogen atmosphere. After stirring for 30 minutes, 3,5-dibromo-pyrazin-2-ylamine (7.08 g, 28.2 mmol) in anhydrous tetrahydrofuran (50 mL) was added via an addition funnel. Once the addition was complete the ice bath was removed and the reaction was refluxed under nitrogen and monitored by reversed phase HPLC. After 18 hr HPLC showed that the majority of the starting 3,5-dibromo-pyrazin-2-ylamine had been consumed and the reaction was allowed to cool to room temperature. The reaction mixture was concentrated in vacuum until 50 mL remained. The mixture was diluted with ethyl acetate (200 mL) and extracted with 50% brine (2×200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuum. The crude product was purified using a silica gel column eluting with 1:1 ethyl acetate/dichloromethane to yield 5-bromo-3-(2,6-dichloro-benzyloxy)-pyrazin-2-ylamine as a white solid (8.17 g, 83% yield).

Example II(b)

5-Bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine was prepared following procedure 2 from (2-chloro-3,6-difluoro-phenyl)-methanol and 3,5-dibromo-pyrazin-2-ylamine.

Example II(c)

1. 2-Chloro-3,6-difluorobenzaldehyde (1.0 molar equivalent) was dissolved in THF (0.2 M) and stirred at 0° C. for 5 min. The corresponding methylmagnesium chloride solution (1.1 molar equivalent) was added The reaction was warmed up gradually to ambient temperature and stirred for 2 hr. Methanol and 1N HCl were added to the mixture and diluted with ethyl_acetate. The mixture was washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give 1-(2-chloro-3,6-difluoro-phenyl)-ethanol as oil. ^1H NMR (400 MHz, DMSO-d_6) δ 1.42 (d, 3H), 5.21 (m, 1H), 5.42 (m, 1H), 7.09 (m, 1H), 7.18 (m, 1H).

2. 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-ylamine was prepared following procedure 2 from 1-(2-chloro-3,6-difluoro-phenyl)-ethanol and 3,5-dibromo-pyrazin-2-ylamine.

Example II(d)

1. 1-(2-Chloro-3,6-difluoro-phenyl)-2-methyl-propan-1-ol was prepared following the procedure of Example II(c) using isopropylmagnesium chloride. ^1H NMR (400 MHz, DMSO-d_6) δ 0.63 (d, 3H), 1.06 (d, 3H), 2.19 (m, 1H), 4.59 (m, 1H), 5.54 (d, 1H), 7.21 (m, 1H), 7.36 (m, 1H).

2. 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-pyrazin-2-ylamine was prepared following procedure 2 from 1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propan-1-ol and 3,5-dibromo-pyrazin-2-ylamine.

Example II(e)

1. 2,6-Dichloro-3-fluoroacetophenone (15 g, 0.072 mol) was stirred in THF (150 mL, 0.5 M) at 0° C. using an ice bath for 10 min. Lithium aluminum hydride (from Aldrich, 2.75 g, 0.072 mol) was slowly added. The reaction was stirred at ambient temperature for 3 h. The reaction was cooled in ice bath, and water (3 mL) was added drop wisely followed by adding 15% NaOH (3 mL) slowly. The mixture was stirred at ambient temperature for 30 min. 15% NaOH (9 mL), $MgSO_4$ were added and the mixture filtered to remove solids. The solids were washed with THF (50 mL) and the filtrate was concentrated to give 1-(2,6-Dichloro-3-fluoro-phenyl)-ethanol (14.8 gm, 95% yield) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 1.45 (d, 3H), 5.42 (m, 2H), 7.32 (m, 1H), 7.42 (m, 1H).

2. 5-Bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-ylamine was prepared following procedure 2 from 1-(2,6-dichloro-3-fluoro-phenyl)-ethanol and 3,5-dibromo-pyrazin-2-ylamine.

Example II(f)

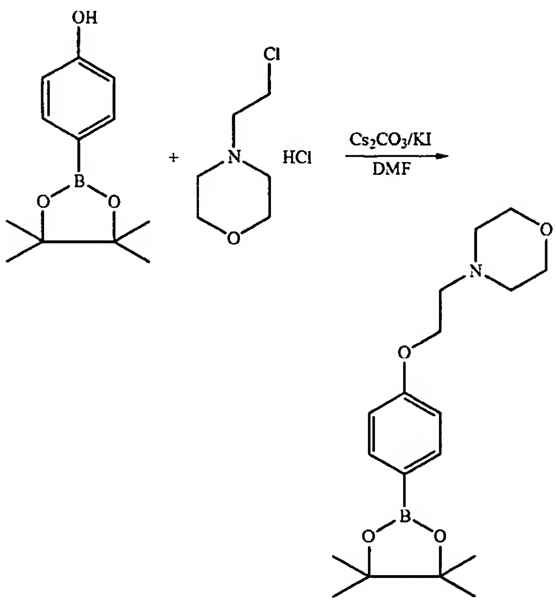
5-Bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-ylamine was prepared following procedure 2 from (3-fluoro-2-trifluoromethyl-phenyl)-methanol and 3,5-dibromo-pyrazin-2-ylamine.

Example I-1

A mixture of 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (example I(a), 100 mg, 0.29 mmol), 4-(4,4,5,5-tetramethyl-1,3-2-dioxabordan-2-yl) phenol (86 mg, 0.35 mmol), bis(triphenylphosphine) palladium(II) chloride (8 mg, 0.009 mmol) and sodium carbonate (91 mg, 0.87 mmol) in ethylene glycol dimethyl ether (10 mL) and water (0.5 mL) was heated to reflux under nitrogen for 18 hours. The reaction was cooled to ambient temperature and diluted with ethyl acetate. The mixture was washed with water, brine, dried over Na_2SO_4, and purified on silica column to afford 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol as light pine crystals (89 mg, 85% yield).

Example I-2

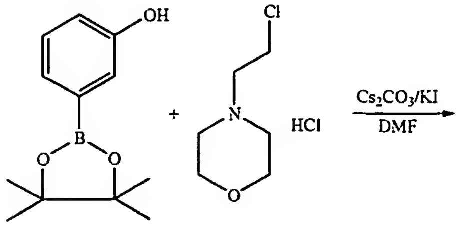
1. To a mixture of 4-(4,4,5,5-tetramethyl-1,3-2-dioxabordan-2-yl) phenol (5.00 g, 22.72 mmol) and Cs_2CO_3 (16.29 g, 49.98 mmol) in DMF (100 mL) were added 4(2-chloroethyl)morpholine hydrochloride (4.65 g, 24.99 mmol) and KI (0.2 g, 0.6 mmol). The mixture was stirred at 65° C. oil bath



for overnight and then cooled to ambient temperature. The reaction mixture was diluted with ethyl acetate (600 mL), and partitioned with water. The water layer was extracted with ethyl acetate (2×50 mL). The combined ethyl acetate solution was washed with brine (5×100 mL), dried over Na_2SO_4, filtered, condensed, and dried in high vacuum to provide 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (6.8 g, 90% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, 2H), 6.90 (d, 2H), 4.07 (t, 2H), 3.54 (m, 4H), 265 (t, 2H), 2.43 (m, 4H).

2. 3-(2,6-Dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (example I(a)) and 4{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (prepared in part 1) following procedure 3 as a white solid.

Example I-3



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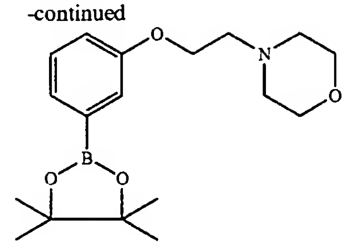
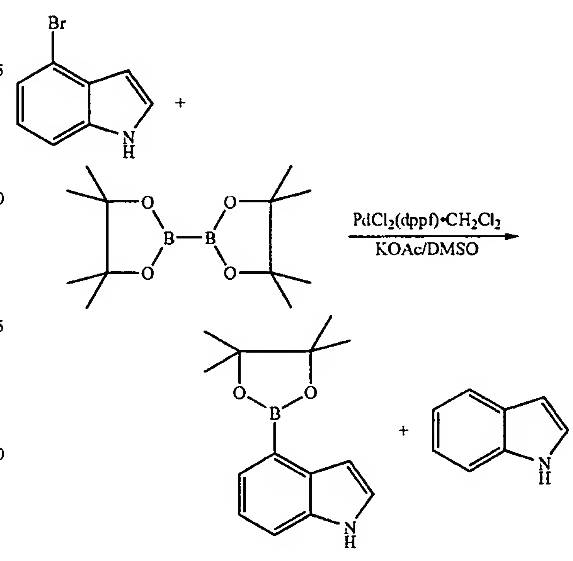


1. 3-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine was prepared following the same procedure as 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine in Example I-2 using 3-(4,4,5,5-tetramethyl-1,3-2-dioxabordan-2-yl) phenol in 92% yield as a white wax solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.28 (t, 1H), 7.22 (dt, 1H), 7.14 (d, 1H), 7.04 (ddd, 1H), 4.06 (t, 2H), 3.56 (m, 4H), 2.49 (t, 2H), 2.45 (m, 4H).

2. 3-(2,6-Dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (example I(a)) and 3-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine prepared in part 1 following procedure 3 as a light yellow solid.

Example I-4



1. To a mixture of 4-bromoindole (9.80 g, 50 mmol), pinacole diborate (13.97 g, 55 mmol), and KOAc (14.72 g, 150 mmol) in DMSO (200 mL) was added palladium catalyst $PdCl_2(dppf)CH_2Cl_2$ (1.22 g, 1.5 mmol). The system was degassed, and then charged with nitrogen for three times. The mixture was stirred at 80° C. oil bath under nitrogen for 22 hours. TLC showed the complete disappearance of the starting material 4-bromoindole. The mixture was cooled to room temperature, and then poured to water (1 L). The product was extracted with ethyl acetate for three times. The combined extracts were washed by brine for five times to remove DMSO solvent, and then dried over

Na_2SO_4. During the washing step, the catalyst may precipitate out, which was removed by filtration. The ethyl acetate solution was filtered and condensed. The residue was purified on a silica gel column eluting with EtOAc-hexane (9:1). The first fraction provided the side product indole (1.25 g, 21% yield), R_f=0.55 (EtOAc-Hexane 5:1). The second fraction provided 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole as a white solid (8.01 g, 66%), R_f 0.46 (EtOAc-Hexane 5:1). ^1H NMR (300 MHz, DMSO-d_6): δ11.03 (bs, 1H, N—H)), 7.49 (d, J=7.7 Hz, 1H, H-5), 7.38 (dd, J=0.9 Hz, J=7.0 Hz, 1H. H-7), 7.38 (t, J=2.6 Hz, 1H, H-2), 7.06 (dd, J=7.7 Hz, J=7.0 Hz, 1H, H-6), 6.73 (bd, J=2.2 Hz; 1H, H-3), 1.32 (s, 12H, 4CH_3); MS (m/e): 244 $(M+H)^+$.

2. 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (Example I(a)) and 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole following procedure 3. The first fraction was identified to be 3-(2,6-dichloro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine.

Example I-5

The same experiment was performed as Example 4, and the second fraction was identified as 3-[2-chloro-6-(1H-indol-4-yl)-benzyloxy]-5-(1H-indol-4-yl)-pyridin-2-ylamine.

Example I-6

2-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-pyrrole-1-carboxylic acid tert-butyl ester was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (Example I(a)) and N-Boc pyrrole-2-boronic acid following procedure 3.

Example I-7

To a mixture of 2-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-pyrrole-1-carboxylic acid tert-butyl ester (Example 6, 30 mg, 0.069 mmol) in ethanol/water (2:1, 10 mL) was added sodium carbonate (100 mg, 0.95 mmol). The mixture was refluxed overnight. The reaction was cooled to ambient temperature and extracted with ethyl acetate. The mixture was washed with water, brine, dried over Na_2SO_4, and purified on a silica gel column to afford 3-(2,6-dichloro-benzyloxy)-5-(1H-pyrrol-2-yl)-pyridin-2-ylamine.

Examples I-8 to I-12

The compounds of Examples I-8 to I-12 were prepared according to procedure 3 using 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and: 4-fluorophenyl boronic acid (Example I-8); phenyl boronic acid (Example I-9); 2-fluorophenyl boronic acid (Example I-10); 3-fluorophenyl boronic acid (Example I-11); and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (Example I-12).

Example I-13

To a solution of 5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (100 mg, 0.28 mmol) in methylene chloride (5 mL) at 0° C., was added methanesulfonyl chloride (0.021 mL, 0.28 mmol) and 4-methylmorpholine (0.16 mL). The mixture was stirred at room temperature for 2 hr, and diluted with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified with a silica gel column eluting with hexane-ethyl acetate (5:1) to give N-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide.

Example I-14

To a solution of 5-(4-amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (100 mg, 0.28 mmol) in acetonitrite (3 mL) at 0° C., was added pyridine (0.035 mL, 1.5 eq.) and acetic anhydride (0.03 mL, 0.28 mmol). The mixture was stirred at room temperature over night, and the precipitate was filtered to provide N-{4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl) acetamide as a white solid.

Examples I-15 to I-35

The compounds of Examples I-15 to I-35 were prepared according to procedure 3 from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and: 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (Example I-15); 4-methoxyphenyl boronic acid (Example I-16); 3-aminobenzeneboronic acid (Example I-17); 4-trifluoromethoxybenzeneboronic acid (Example I-18); 2-hydroxybenzene boronic acid (Example I-19); 2-phenoxyphenylboronic acid (Example I-20); 3,4-difluorophenylboronic acid (Example I-21); (3-isopropyl)phenylboronic acid (Example I-22); (2-trifluoromethylphenyl)boronic acid (Example I-23); (2-methoxyphenyl)boronic acid (Example I-24); (4-trifluoromethylphenyl)boronic acid (Example I-25); [(2-methylsulfonylamino)phenyl]boronic acid (Example I-26); 4-hydroxymethylphenylboronic acid (Example I-27); 3,4-methylenedioxyphenylboronic acid (Example I-28); 2-trifluoromethoxyphenylboronic acid (Example I-29); 4-methylthiophene-2-boronic acid (Example I-30); 2-benzyloxyphenylboronic acid (Example I-31); 3-methoxyphenylboronic acid (Example I-32); 1-(tert-butoxycarbonyl)indole-2-boronic acid, and the tert-butoxycarbonyl group was removed using 20% trifluoroacetic acid in dichloromethane (Example I-33); (3-fluoro-4-benzyloxyphenyl) boronic acid (Example I-34); and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Example I-35).

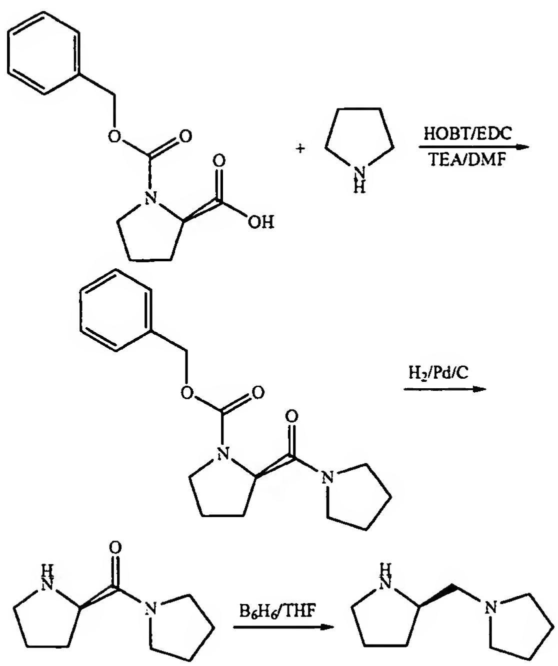
Example I-36

To a solution of 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid (50 mg, 0.13 mmol), HOBT (21 mg, 0.156 mmol), and EDC (30 mg, 0.156 mmol) in DMF (2 mL) was added N,N-diethylethylenediamine (0.022 mL, 0.156 mmol). The reaction was stirred at room temperature for 24 hr, then diluted with EtOAc, and partitioned with H_2O. The organic was separated and the aqueous was extracted with EtOAc. The organic layers were combined, washed with saturated $NaHCO_3$, and concentrated to dryness under vacuum. The material was purified using column chromatography (silica gel, 99:1 to 95:5 CH_2Cl_2/MeOH) to give 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-diethylamino-ethyl)-benzamide (45 mg, 72% yield) as a white solid.

Examples I-37 and I-38

The compounds of Examples I-37 and I-38 were prepared from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and N,N-diethyl-1,3-propanediamine (Example I-37) and 1-methylpiperazine(Example I-38), following procedure 4.

Example I-39



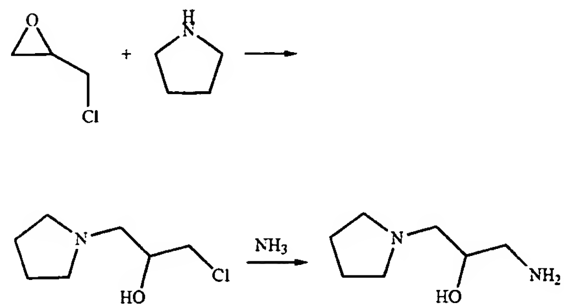
1. A mixture of (+)-carbobenzyloxy-D-proline (1.5 g, 6 mmol), EDC (2.3 g, 12 mmol), HOBt (800 mg, 6 mmol), TEA (1.5 mL) and pyrrolidine (853 mg, 12 mmol) in DMF (20 mL) was stirred at rt for 18 hr. The reaction was diluted with water and sodium bicarbonate, extracted with dichloromethane (3×). The combined DCM was concentrated and purified on a silica gel column to give (R)-2-(pyrrolidine-1-carbonyl)-pyrrolidine-1-carboxylic acid benzyl ester. (R)-2-(pyrrolidine-1-carbonyl)-pyrrolidine-1-carboxylic acid benzyl ester was hydrogenated using Pd/C in methanol at ambient temperature for 20 hr to provide pyrrolidin-1-yl-(R)-pyrrolidin-2-yl-methanone. To a solution of pyrrolidin-1-yl-(R)-pyrrolidin-2-yl-methanone (1.2 g, 7.1 mmol) in THF (10 mL) at 0° C. was added B_2H_6 (10 mL, 10 mmol). The mixture was heated to reflux for 16 hr. The reaction was acidified with HCl and concentrated. The residue was basified to pH 10 with 2N NaOH and extracted with 5% methanol in DCM. The organic layer was concentrated and purified on a silica gel column to give 800 mg (73%) of (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine.

2. {4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Examples I-40 to I-45

The compounds of Examples I-40 to I-45 were prepared according to procedure 4 from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-40); 4-pyrrolidin-1-yl-piperidine (Example I-41); 4-piperidine ethanol (Example I-42); (3S)-(3-dimethylamino-pyrrolidine (Example I-43); (3R)-(3-dimethylamino-pyrrolidine (Example I-44); and (S)-3-cyclopropylaminomethyl-piperidine (prepared according to the procedures for (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine in example I-39) (Example I-45).

Example I-46



1. To a solution of epichlorohydrin (from Aldrich, Milwaukee, 3.91 mL, 50.0 mmol) in EtOH (100 mL) was added pyrrolidine (4.18 mL, 50.0 mmol) at room temperature. The mixture was stirred at 55~60° C. for 20 hr, then refluxed for 3 hr. The solvent was removed under reduced pressure and crude 1-chloro-3-pyrrolidin-1-yl-propan-2-ol was obtained as an oil (10 g). This oily product was dissolved in 7 M ammonia in MeOH (40 mL) and stirred at room temperature overnight. Then another 30 mL of 7 M ammonia in MeOH was added and the mixture was stirred at 40° C. overnight. NMR showed that the starting material disappeared completely. The solvent was removed and the residue was dissolved in 2 N HCl and then lyophilized to give 10.8 g of oil salt product, which was dissolved in MeOH—H_2O at 0° C. and the resin (AG1-X8, hydroxide form) was added in portions with stirring until the pH of the solution is above 9.0. After filtration, the filtrate was evaporated under reduced pressure to give the free amine 1-amino-3-pyrrolidin-1-yl-propan-2-ol as yellowish oil (8.6 g). This crude product was used for the reaction without further purification.

2. 4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide was prepared from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and 1-amino-3-pyrrolidin-1-yl-propan-2-ol following procedure 4.

Examples I-47 to I-52

The compounds of Examples I-47 to I-52 were prepared according to procedure 4 from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and: 3-fluoro-1-(2S)-pyrrolidin-2-ylmethyl-piperidine (prepared according to the procedures for (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine) (Example I-47); 1-cyclopropyl-piperazine (Example I-48); (R)-2-[(cyclopropylmethyl-amino)-methyl]-pyrrolidine (prepared according to the procedures for (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine) (first fraction, Example I-49; second fraction, Example I-50); N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-N-methyl amine (prepared according to the same procedure as 1-amino-3-pyrrolidin-1-yl-propan-2-ol (Example I-51); and (2S)-2-[(3R)-3-hydroxy-pyrrolidin-1-ylmethyl)-pyrrolidine (prepared according to the procedure for (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine) (Example I-52).

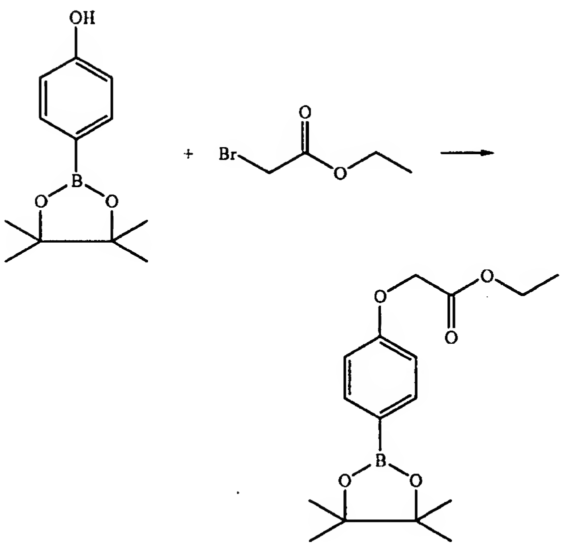
Example I-53

3-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and 3-(4,4,5,5-tetramethyl-(1,3,2]dioxaborolan-2-yl)-benzoic acid following procedure 3.

Example I-54

{3-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-Yl) phenyl)(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared from 3-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Example I-55



1. To a solution of 4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-phenol (10.0 g, 45.5 mmol) and Cs_2CO_3 (23.5 g, 68.25 mmol) in DMF (60 mL) was added ethyl α-bromoacetate (11.6 g, 68.25 mmol). The mixture was stirred at room temperature for 24 hours, then diluted with-ethyl acetate, washed with water, dried over Na_2SO_4. After filtration and evaporation, the residue was dried under high vacuum to provide [4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-phenoxy]-acetic acid ethyl ester (12.52 g, 90% yield) as an oil.

2. A mixture of 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine (Example I(a)) (2.2 g, 6.3 mmol), [4-(4,4,5,5-tetramethyl-(1,3]dioxolan-2-yl)-phenoxy]-acetic acid ethyl ester (2.9 g, 1.5 eq.), bis(triphenylphosphine)palladium (II) chloride (136 mg) and sodium carbonate (1.93 g, 3.0 eq.) in ethylene glycol dimethyl ether (30 mL), DMF (5 mL) and water (8 mL) was heated to 90–100° C. under nitrogen for 7 hr. The reaction was cooled to rt and diluted with ethyl acetate. The mixture was washed with water, brine, dried and purified on silica column to afford (4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid ethyl ester. This ester was treated with sodium carbonate and water at rt overnight. The reaction was diluted with ethyl acetate. The mixture was washed with water, brine, dried and purified on silica column to afford 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid.

Example I-56

2-(4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone was prepared from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid and (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Example I-57

2-{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone was prepared from 4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid and (S)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Example I-58

3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and indole-5-boronic acid following procedure 3.

Example I-59

To a solution of 3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine (example I-58, 200 mg, 0.52 mmol) in acetic acid (4 mL) and trifluoroacetic-acid (1 mL) was added 1-methyl-4-piperidone (0.32 mL, 2.6 mmol). The solution was refluxing for over night, and evaporated. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and condensed. The crude product was purified on a silica gel column eluting with dichloromethane-methanol-triethyl amine (95:5:0.1) to provide 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine (103.5 mg, 41% yield) as an orange crystalline solid.

Example I-60

To a de-gassed solution of 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine (example I-61, 130 mg, 0.27 mmol) in methanol (50 mL) and acetic acid (5 mL) was added 10% Pd/C (50 mg). The solution was degassed and charged with hydrogen for three times, and then was stirred under hydrogen balloon-for over night. The mixture was filtered through a celite pad, washed with methanol, and then condensed. The residue was dissolved in ethyl acetate, washed with sat. NaHCO3 and brine, dried over Na_2SO_4, and condensed. The crude product was purified on a silica gel column eluting with dichloromethane-methanol-triethyl amine (95:5:0.1) to provide 3-(2,6-dichloro-benzyloxy)-5-[3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine as a white solid.

Examples I-61–I-68

The compounds of Examples I-61 to I-68 were prepared according to procedure 5 from 3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine and: morpholine (Example I-61); piperidine (Example I-62); pyrrolidine (Example I-63); diethylamine (Example I-64); pyrrolidin-3-yl-carbamic acid tert-butyl ester (Example I-65); 2,6-dimethyl-

morpholine following (Example I-66); (R)-pyrrolidin-3-yl-acetamide (Example I-67); and piperazin-1-yl-ethanone (Example I-68).

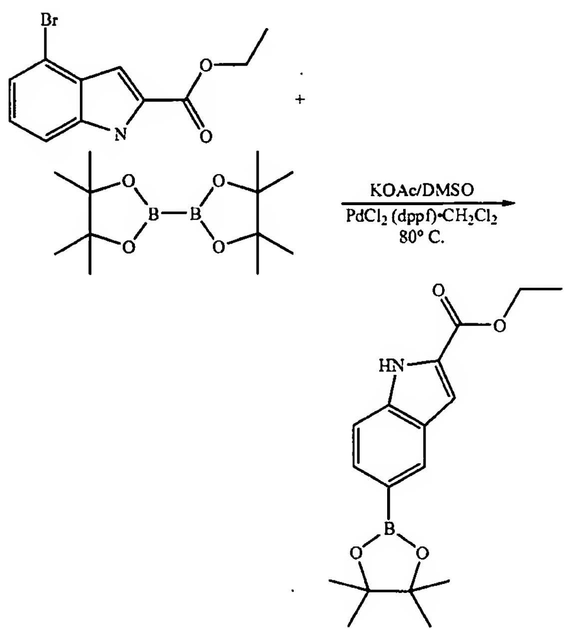
Example I-69

3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine was prepared from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and indole-5-boronic acid following procedure 3.

Examples I-70 to I-75

The compounds of Examples I-70 to I-75 were prepared according to procedure 5 from 3-(2-chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine and: piperazin-1-yl-ethanone (Example I-70); 2,6-dimethyl-morpholine (Example I-71); (3S)-pyrrolidin-3-yl-acetamide (Example I-72); piperidine (Example I-73); morpholine (Example I-74); and pyrrolidine (Example I-75).

Example I-76



1. To a stirred solution of ethyl 5-bromo-1H-indole-2-carboxylate (5 g, 18.6 mmol) in DMSO (75 mL, 0.25 M), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (11.2 g, 44.3 mmol), potassium acetate (5.5 g, 56.0 mmol), and [bis(diphenylphosphino)ferrocene]dichloropalladium 11 (1.23 mmol) were added. The mixture was de-gassed and charged with nitrogen for three times, and then heated at 80° C. under nitrogen for overnight. The reaction was cooled to ambient temperature and diluted with ethyl acetate (2×100 mL). The mixture was washed with water (1×50 mL), brine (1×50 mL), dried over $MgSO_4$, and purified on a silica gel column to afford ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxylate as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 1.31 (t, 3H), 4.32 (m, 2H), 7.18 (s, 1H), 7.42 (d, 1H), 7.54 (d, 1H), 8.05 (s, 1H), 11.96 (s, 1H); MS IT/z 315 (M+1).

2. 5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid ethyl ester was prepared from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole-2-carboxylic acid ethyl ester following procedure 3.

Example I-77

To a mixture of ethyl 5-{6-amino-5-[(2,6-dichlorobenzyl)oxy]pyridin-3-yl)11H-indole-2-carboxylate (2.5 g, 5.5 mmol) in methanol:water (60 mL 20 mL), lithium hydroxide (0.65 g, 27.1 mmol) was added. The reaction was heated to reflux for overnight. Most of the solvent was evaporated and the mixture was acidified, and stirred for 10 min. The precipitate was filtered out and washed with water to yield 5-{6-amino-5-[(2,6-dichlorobenzyl)oxy]pyridin-3-yl)-1H-indole-2-carboxylic acid as tan solid.

Examples I-78 to I-85

The compounds of Examples I-78 to I-85 were prepared according to procedure 4 from 5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid and: N-methylpiperazine (Example I-78); (3R)-3-dimethylamino-pyrrolidine (Example I-79); (2R)-2-pyrrolidin-1-yl-methyl-pyrrolidine (prepared as in example I-39) (Example I-80); 2-pyrrolidin-1-yl-ethylamine (Example I-81); 2-morpholin-4-yl-ethylamine (Example I-82); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (Example I-83), followed by de-protection of the Boc-group in 20% trifluoroacetic acid in dichloromethane (Example I-84); 2-hydroxy-3-pyrrolidin-1-yl-propylamine (Example I-85).

Example I-86

4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenol was prepared from 3-benzyloxy-5-bromo-pyridin-2-ylamine and 4-(4,4,5,5-tetramethyl-1,3-2-dioxabordan-2-yl) phenol following procedure 3.

Example I-87

3-Benzyloxy-5-phenyl-pyridin-2-ylamine was prepared from 3-benzyloxy-5-bromo-pyridin-2-ylamine and phenylboronic acid following procedure 3.

Example I-88

3-(3-Methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine was prepared according to procedure 6.

Examples I-89 to I-105

The compounds of Examples I-89 to I-105 were prepared according to procedure 6 from: 2-chloro-4-fluoro-benzylbromide (Example I-89); 2-chlorobenzylbromide (Example I-90); 2,5-dichlorobenzylbromide (Example I-91); 2-chloro-5-trifluoromethyl benzylbromide (Example I-92); 2,4-Dichloro-5-fluoro-benzylbromide (Example I-93); 2-chloro-3-trifluoromethyl-benzylbromide (Example I-94); 2-chloro-3,6-difluoro-benzylbromide (Example I-95); 3,4-dichlorobenzylbromide (Example I-96); 2-bromomethyl-benzonitrile (Example I-97); 2-chloro-6-fluoro-3-methyl-benzylbromide (Example I-98); 2-bromomethyl-1,3,4-trifluoro-benzene (Example I-99); 2-bromomethyl-1,3-difluoro-benzene (Example I-100); 2-bromomethyl-1,3-difluoro-4-methyl-benzene (Example I-101); 2-bromomethyl-4-chloro-1,3-difluoro-benzene (Example I-102); 2-bromomethyl-1-chloro-3-fluoro-benzene (Ex-

ample I-103); 4-bromomethyl-2-fluoro-1-methoxy-benzene (Example I-104); and 1-bromomethyl-3-nitro-benzene, followed by reduction of the nitro group to amino and reaction with methanesulfonyl chloride (Example I-105).

Example I-106

5-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-3-(3-nitro-benzyloxy)-pyridin-2-ylamine was synthesized according to procedure 7.

Examples I-107 to I-110

The compounds of Examples I-107 to I-110 were prepared according to procedure 7 from: 1-bromomethyl-naphthalene (Example I-107); 2-bromomethyl-3-chloro-1,4-difluoro-benzene (Example I-108); 2-bromo-N-(4-isopropyl-phenyl)-2-phenyl-acetamide (Example I-109); and 3-bromomethyl-5-chloro-benzo[b]thiophene (Example I-110).

Example I-111

{4-[6-Amino-5-(4-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl{-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was synthesized according to procedure 8.

Examples I-112 to I-117

The compounds of Examples I-112 to I-117 were prepared according to procedure 8 from: 2-bromomethyl-1-fluoro-3-trifluoromethyl-benzene (Example I-112); 2-bromomethyl-4-fluoro-1-trifluoromethyl-benzene (Example I-113); 1-(1-bromo-ethyl)-2-trifluoromethyl-benzene (Example I-114); 1-bromo-2-bromomethyl-benzene (Example I-115); 1-bromomethyl-3-fluoro-2-trifluoromethyl-benzene (Example I-116); and 2-bromomethyl-3-chloro-1,4-difluoro-benzene (Example I-117).

Examples I-118 to I-121

The compounds of Examples I-118 to I-121 were prepared according to procedure 3 from 5-bromo-3-(2,6-difluoro-benzyloxy)-pyridin-2-ylamine and: 4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-phenol (Example I-118); 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (Example I-119); 4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-1H-indole (Example I-120); and 4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-benzoic acid (Example I-121).

Example I-122

{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared from 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Example I-123

{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared from 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Example I-124

{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid ethyl ester was prepared from 5-bromo-3-(2,6-difluoro-benzyloxy)-pyridin-2-ylamine and of [4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-phenoxy]-acetic acid ethyl ester following procedure 3.

Example I-125

{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid ethyl ester (1.0 g, 2.41 mmol) was treated with sodium carbonate (1.28 g, 12.05 mmol) and water (10 mL) at 90–100° C. overnight. The reaction was cooled to rt and diluted with ethyl acetate. The mixture was washed with water, brine, dried and purified on silica column to afford 4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid.

Example I-126

2-{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy)-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone was prepared from 4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy)acetic acid and (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

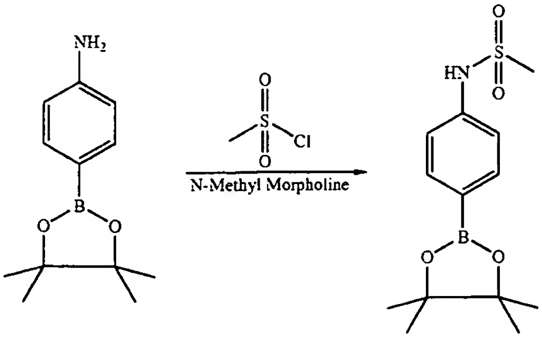
Example I-127

2-{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone was prepared from 4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid and (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine following procedure 4.

Examples I-128 to I-134

The compounds of Examples I-128 to I-134 were prepared according to procedure 3 from 4-(4,4,5,5-tetramethyl-[1,3]dioxolan-2-yl)-phenol and: 5-bromo-3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine (Example I-128); 5-bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine (Example I-129); 5-bromo-3-(2,4-dichloro-benzyloxy)-pyridin-2-ylamine (Example I-130); 2-(2-amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile (Example I-131); 5-bromo-3-(2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine (Example I-132); 5-bromo-3-(2-chloro-benzyloxy)-pyridin-2-ylamine (Example I-133); and 5-bromo-3-(4-tert-butyl-benzyloxy)-pyridin-2-ylamine (Example I-134).

Example I-135



1. To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (5.00 g, 22.8 mmol) in methylene chloride (100 mL) and 4-methylmorpholine (16 mL) at 0° C. was added methanesulfonyl chloride (2.1 mL, 28 mmol). The mixture was stirred at room temperature for 2 hr, and diluted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to provide N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide as a white solid (6.32 g, 93% yield). MS m/z 298 (M+1).

2. N-{4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide was prepared following procedure 3 from 2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile and N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide.

Example I-136

10% NaOH solution (25 mL) was added to N-{4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-phenyl)methanesulfonamide (Example I-135, 650 mg, 1.65 mmol) in ethylene glycol (55 mL). The mixture was heated to reflux and allowed to stir for 24 hr. The reaction was cooled to room temperature. Most of the solvent was evaporated and the mixture was acidified. The precipitated solid was filtered out to afford 2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzoic acid as light brown solid. The filtrate was neutralized and extracted with EtOAc (5×20 mL). The organic layer was combined, dried over $MgSO_4$, and concentrated to yield 2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzamide as an off-white solid.

Example I-137

2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzoic acid was prepared as in Example I-136.

Example I-138 to I-140

The compounds of Examples I-138 to I-140 were prepared according to procedure 4 from 2-[2-amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzoic acid and: N-methyl-piperazine (Example I-138); 2-hydroxyethylamine (Example I-139); and isobutylamine (Example I-140).

Example I-141

5-Bromo-3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine (Example I(e), 9.00 g, 27.0 mmol), 4-carboxybenzeneboronic acid (4.41 g, 27.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.99 g, 0.9 mmol), potassium carbonate (13.1 g, 95.0 mmol), dimethylformamide (72 mL) and water (36 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81° C. to 98° C. over a period of 4 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed a trace of starting material at Rf 0.7, product at Rf 0.4 and many small impurities. The mixture was cooled to 45° C. The solids were collected by vacuum filtration, washed with 30 mL of ethanol:water 1:1 and discarded. The filtrate was diluted with 432 mL of water and 8 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes. The solids were collected by vacuum filtration and washed with 5 mL of water. The filtrate was cooled in an ice bath and acidified to pH 7.5 with acetic acid using a pH meter. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and dried under vacuum to give 2.5 g of 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and a second compound as a brown solid in a ratio of about 1:1 by ^{1}H-NMR. This material was discarded. The filtrate was acidified to pH 6.5 with acetic acid using a pH meter. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and dried under vacuum to give 3.6 g (36% yield) of 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid as a brown solid containing a 5–10% impurity by ^{1}H-NMR.

Examples I-142 to I-149

The compounds of Examples I-142 to I-149 were prepared according to procedure 4 from 4-[6-amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-142); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-143); (3S)-3-dimethylamino-pyrrolidine (Example I-144); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-145); N-methylpiperazine (Example I-146); 1-piperazin-1-yl-ethanone (Example I-147); 2-morpholin-4-yl-ethylamine (Example I-148); 3-morpholin-4-yl-propylamine (Example I-149).

Example I-150

5-Bromo-3-(2-chloro-benzyloxy)-pyridin-2-ylamine (4.50 g, 14.3 mmol), 4-carboxybenzeneboronic acid (2.62 g, 15.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.5 mmol), potassium carbonate (6.90 g, 50 mmol), dimethylformamide (36 mL), and water (18 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 82 to 93° C. over a period of 4 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed product at Rf 0.3 and a few small impurities. The mixture was cooled to 45° C. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and discarded. The combined filtrate was diluted with 216 mL of water and 4 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes with 3 g of Celite and 3 g of Norit. The solids were collected by vacuum filtration through a pad of Celite and washed with 10 mL of water. The solids were discarded. The combined filtrate was cooled in an ice bath and acidified to pH 7 with acetic acid using a pH meter. The solids were collected by vacuum filtration, washed with 20 mL of ethanol:water 1:1 and dried under vacuum to give 2.7 g (53% yield) of 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoic acid.

Examples I-151 to I-159

The compounds of Examples I-151 to I-159 were prepared according to procedure 4 from 4-[6-amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-151); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-152); (3S)-3-dimethylamino-pyrrolidine (Example I-153); pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane

(Example I-154); 4-pyrrolidin-1-yl-piperidine (Example I-155); N-methylpiperazine (Example I-156); 1-piperazin-1-yl-ethanone (Example I-157); 2-morpholin-4-yl-ethylamine (Example I-158); and 3-morpholin-4-yl-propylamine (Example I-159).

Example I-160

2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile (9.0 g, 29.6 mmol), 4-carboxybenzeneboronic acid (5.4 g, 32.5 mmol), tetrakis(triphenylphosphine)palladium(0) (1.1 g, 1.0 mmol), anhydrous potassium carbonate (13.8 g, 70.0 mmol), dimethylformamide (72 mL) and water (36 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81 to 90° C. over a period of 2 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed a trace of starting material at Rf 0.7, product at Rf 0.4 and an impurity at Rf 0.5. The mixture was cooled to 45° C. The sticky solids were collected by vacuum filtration, washed with 30 mL of ethanol:water 1:1 and discarded. The filtrate was diluted with 432 mL of water and 8 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes. The solids were collected by vacuum filtration and washed with 20 mL of water. The solids were discarded. The filtrate was cooled in an ice bath acidified with acetic acid to pH 7.5 using a pH meter. The solids were collected by vacuum filtration, washed with 20 mL water and dried under vacuum to give 8.5 g (83% yield) of 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-benzoic acid as a very dark solid.

Examples I-161 to I-170

The compounds of Examples I-161 to I-170 were prepared according to procedure 4 from 4-[6-amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-161); (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-162); (3S)-3-dimethylamino-pyrrolidine (Example I-163); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-164); 4-pyrrolidin-1-yl-piperidine (Example I-165); N-methylpiperazine (Example I-166); 1-piperazin-1-yl-ethanone (Example I-167); 1-methyl-piperidin-4-ylamine (Example I-168); 2-Morpholin-4-yl-ethylamine (Example I-169); and 3-morpholin-4-yl-propylamine (Example I-170).

Example I-171

5-Bromo-3-(2,4-dichloro-benzyloxy)-pyridin-2-ylamine (6.96 g, 20.0 mmol), 4-carboxybenzeneboronic acid (3.98 g, 24.0 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.74 g, 0.66 mmol), potassium carbonate (9.7 g, 70 mmol), dimethylformamide (35 mL)-and water (17 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81 to 95° C. over a period of 9 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed a trace of starting material at Rf 0.7, product at Rf 0.4 and impurities at Rf 0.5 and 0.3. The mixture was cooled to room temperature and allowed to stand over for about 48 hr. The solids were collected by vacuum filtration, washed with 30 mL of ethanol:water 1:1 and saved. The filtrate was diluted with 210 mL of water and 8 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes. The solids were collected by vacuum filtration and washed with 5 mL of water to give about 1 g of a mixture of product and a spot running with starting material. This mixture was discarded. The filtrate was cooled in an ice bath and acidified to pH 5–6 with about 10 mL of acetic acid. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and dried under vacuum to give 2.9 g (37% yield) of 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid as a brown solid.

Examples I-172 to I-181

The compounds of Examples I-172 to I-181 were prepared according to procedure 4 from 4-[6-amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-172); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-173); (3S)-3-dimethylamino-pyrrolidine (Example I-174); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-175); 4-pyrrolidin-1-yl-piperidine (Example I-176); N-methylpiperazine (Example I-177); 1-piperazin-1-yl-ethanone (Example I-178); 1-methyl-piperidin-4-ylamine (Example I-179); 2-morpholin-4-yl-ethylamine (Example I-180); and 3-morpholin-4-yl-propylamine (Example I-181).

Example I-182

5-Bromo-3-(2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine (5.80 g, 16.7 mmol), 4-carboxybenzeneboronic acid (3.05 g, 18.4 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.62 g, 0.6 mmol), potassium carbonate (8.10 g, 58 mmol), dimethylformamide (47 mL) and water (23 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81 to 93° C. over a period of 4 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed product at Rf 0.6 and a few small impurities. The mixture was cooled to 45° C. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and discarded. The filtrate was diluted with 300 mL of water and 4 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes with 3 g of Celite and 3 g of Norit. The solids were collected by vacuum filtration through a pad of Celite and washed with 10 mL of water. The solids were discarded. The filtrate was cooled in an ice bath and acidified to pH 7.3 with acetic acid using a pH meter. The solids were collected by vacuum filtration, washed with 20 mL of ethanol:water 1:1 and dried under vacuum to give 4.5 g (69% yield) of 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid as a brown solid.

Examples I-183 to I-192

The compounds of Examples I-183 to I-192 were prepared according to procedure 4 from 4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-183); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-184); (3S)-3-dimethylamino-pyrrolidine (Example I-185); pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-

protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-186); 4-pyrrolidin-1-yl-piperidine (Example I-187); N-methylpiperazine (Example I-188); 1-piperazin-1-yl-ethanone (Example I-189); 1-methyl-piperidin-4-ylamine (Example I-190); 2-morpholin-4-yl-ethylamine (Example I-191); and 3-morpholin-4-yl-propylamine (Example I-192).

Example I-193

2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile (9.0 g, 26.8 mmol), 4-carboxybenzeneboronic acid (4.9 g, 30.0 mmol), tetrakis(triphenylphosphine)-palladium(0) (1.1 g, 1.0 mmol), anhydrous potassium carbonate (13.1 g, 95 mmol), dimethylformamide (72 mL), and water (36 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81 to 96° C. over a period of 2 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed a trace of starting material at Rf 0.8, product at Rf 0.5 and an impurity at Rf 0.4. The mixture was cooled to 45° C. and filtered to remove the solids. The filtrate was diluted with 432 mL of water and 8 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and 4 g of Celite and 2 g of Norit were added. The solids were collected by vacuum filtration through 4 g of Celite, washed with 30 mL of ethanol:water 1:1 and discarded The filtrate was cooled in an ice bath and acidified with acetic acid to pH 7.5 using a pH meter. The solids were collected by vacuum filtration, washed with 20 mL water and dried under vacuum to give 8.1 g (80% yield) 4-[6-amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoic acid as a dark solid.

Examples I-194 to I-201

The compounds of Examples I-194 to I-201 were prepared according to procedure 4 from 4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-194); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-195); (3S)-3-dimethylamino-pyrrolidine (Example I-196); N-methylpiperazine (Example I-197); 1-piperazin-1-yl-ethanone (Example I-198); 1-methyl-piperidin-4-ylamine (Example I-199); 2-morpholin-4-yl-ethylamine (Example I-200); and 3-morpholin-4-yl-propylamine (Example I-201).

Example I-202

5-Bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine (9.00 g, 27.0 mmol), 4-carboxybenzeneboronic acid (4.41 g, 27.0 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.99 g, 0.9 mmol), potassium carbonate (13.1 g, 95 mmol), dimethylformamide (72 mL), and water (36 mL) were charged to a 250 mL three neck round bottom flask equipped with a thermometer, a reflux condenser and magnetic stirring. The mixture was purged with nitrogen and gradually heated from 81 to 98° C. over a period of 4 hr. Thin layer chromatography (ethyl acetate:hexane:acetic acid 4:6:0.5) showed a trace of starting material at Rf 0.7, product at Rf 0.4 and a few small impurities. The mixture was cooled to 45° C. The solids were collected by vacuum filtration, washed with 20 mL of ethanol:water 1:1 and discarded. The filtrate was diluted with 432 mL of water and 8 mL of 9 N potassium hydroxide solution (to pH 12–13), cooled in an ice bath and stirred for 30 minutes. The-solids were collected by vacuum filtration and washed with 5 mL of water to give about 1 g of a mixture which was discarded. The filtrate was cooled in an ice bath and acidified to pH 6.5 with acetic acid using a pH meter. The solids were collected by vacuum filtration, washed with 10 mL of ethanol:water 1:1 and dried under vacuum to give 3.6 g (36% yield) 4-[6-amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid as a brown solid.

Examples I-203 to I-210

The compounds of Examples I-203 to I-210 were prepared according to procedure 4 from 4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-203); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-204); (3S)-3-dimethylamino-pyrrolidine (Example I-205); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-206); N-methylpiperazine (Example I-207); 1-piperazin-1-yl)-ethanone (Example I-208); 2-morpholin-4-yl-ethylamine (Example I-209); and 3-morpholin-4-yl-propylamine (Example I-210).

Example I-211

4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid methyl ester was prepared following procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid as an off-white solid in 55% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 (s, 3H), 4.79 (brs, 2H), 5.29–5.30 (d, 2H, J, 1.6), 7.06–7.19 (dt, 1H, J, 4.1, 9.0), 7.2–7.26 (m, 1H), 7.37–7.38 (d, 1H, 1.8), 7.58–7.61 (m, 2H), 8.01–8.02 (d, 2H, J, 1.8), 8.08–8.11 (m, 2H).

To a stirred solution of 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid methyl ester (2.5 g, 6 mmol) in warm isopropanol (300 mL) was added H_2O (100 mL) containing LiOH (0.74 g, 31 mol). The reaction immediately turned orange and was left to stir at room temperature for 18 hr. The reaction was diluted with EtOAc (200 mL) and brine (50 mL). The organic was separated off and the aqueous was extracted with EtOAc (2×50 mL). The organic layers were combined and washed with brine (2×25 mL), dried with Na_2SO_4 and concentrated to dryness under vacuum to yield 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid (2.4 g, 6 mmol, 99%) as an off-white solid.

Examples I-212 to I-224

The compounds of Examples I-212 to I-224 were prepared according to procedure 4 from 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and: N-methylpiperazine (Example I-212); 4-pyrrolidin-1-yl-piperidine (Example I-213); piperidin-4-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-214); 3,5-dimethyl-piperazine (Example I-215); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-216); (3S)-3-dimethylamino-pyrrolidine (Example I-217); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-218); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-219); 1-methyl-piperidin-4-ylamine (Example I-220); 2-pyrrolidin-1-yl-ethylamine (Example I-221); 3-pyrrolidin-1-yl-

propylamine (Example I-222); 2-morpholin-4-yl-ethylamine (Example I-223); and 3-morpholin-4-yl-propylamine (Example I-224).

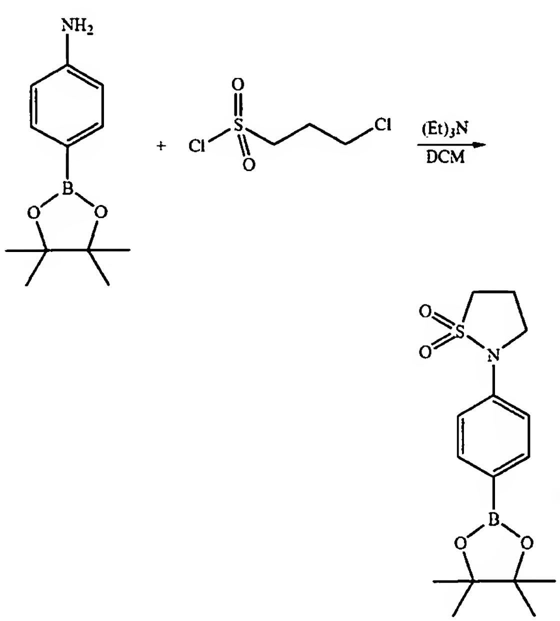
Example I-225

3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

Examples I-226 to I-239

The compounds of Examples I-226 to I-239 were prepared according to procedure 4 from 3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid and: N-methylpiperazine (Example I-226); 4-pyrrolidin-1-yl-piperidine (Example I-227); piperidin-4-yl-carbamic acid tert-butyl ester, and then followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-228); 3,5-dimethyl-piperazine (Example I-229); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-230); (3S)-3-dimethylamino-pyrrolidine (Example I-231); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-232); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-233); 1-methyl-piperidin-4-ylamine (Example I-234); 2-pyrrolidin-1-yl-ethylamine (Example I-235); 3-pyrrolidin-1-yl-propylamine (Example I-236); 2-morpholin-4-yl-ethylamine (Example I-237); 3-morpholin-4-yl-propylamine (Example I-238); and 1-[4-(2-amino-ethyl)-piperazin-1-yl]-ethanone (Example I-239).

Example I-240



1. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5 g, 22.8 mmol) was dissolved in DCM (100 mL, 0.2 M), triethylamine (15 mL, 5.0 molar equivalent) was added to the mixture. The reaction was stirred at 0° C. for 5 min. 3-chloropropane-1-sulfonyl chloride (4.2 g, 23.0 mmol) was added portion wise. The reaction was stirred at 0° C. for 1 hr and brought gradually to room temperature, heated to reflux at 70° C. for 2 hr. The mixture was cooled to room temperature, diluted with EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified through a silica column to afford 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]isothiazolidine 1,1-dioxide as off-white solid (5.2 g, 70% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, 2H), 7.18 (d, 2H), 3.76 (t, 2H), 3.53 (t, 2H), 2.41 (t, 2H), 1.28 (s, 12H).

2. 3-(2-Chloro-3,6-difluoro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine was prepared following procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]isothiazolidine 1,1-dioxide.

Example I-241

3-(2,6-Dichloro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine was prepared following procedure 3 from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]iso-thiazolidine 1,1-dioxide.

Example I-242

5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-3-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-2-ylamine was prepared according to procedure 8.

Example I-243

2-Diethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}amide was synthesized according to procedure 9.

Examples I-244 to I-266

The compounds of Examples I-244 to I-266 were prepared following procedure 9.

Examples I-267 to I-269

The compounds of Examples I-267 to I-269 were prepared according to procedure 3, with purification by reversed phase preparative HPLC eluting with acetonitrile-water-trifluoroacetic acid system and obtained as trifluoroacetic acid salts, from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and: 2-(dimethylaminomethyl)-phenylboronic acid (Example I-267); 3-(pyrrolidin-1-yl)-phenylboronic acid (Example I-268) and-N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanesulfonamide (Example I-269).

Example I-270

5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid was prepared following procedure 3 starting from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-2-ylamine and 5-carboxythiophene-2-boronic acid.

Examples I-271 to I-276

Examples I-271 to I-276 were prepared according to procedure 4 from 5-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid and: N-methylpiperazine (Example I-271); (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-272); 1-methyl-piperidin-4-yl)-amine (Example I-273); 3,5-dimethyl-piperazine (Example I-274); 2-pyrrolidin-1-yl-ethylamine (Example I-275); and 4-pyrrolidin-1-yl-piperidine (Example I-276).

Example I-277

4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-y]-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Examples I-278 to I-285

Examples I-278 to I-285 were prepared according to procedure 4 from 4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid and: 4-pyrrolidin-1-yl-piperidine (Example I-278); 1-methyl-piperidin-4-ylamine (Example I-279); 3,5-dimethyl-piperazine (Example I-280); 3-dimethylamino-pyrrolidine (Example I-281); (2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-282); 2-morpholin-4-yl-ethylamine (Example I-283); N-methylpiperazine (Example I-284); and 4-acetyl-piperazin-1-yl)-ethylamine (Example I-285).

Examples I-286 to I-289

The compounds of Examples I-286 to I-289 were prepared following procedure 9.

Example I-290

4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Examples I-291 to I-296

The compounds of Examples I-291 to I-296 were prepared according to procedure 4 from 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}benzoic acid and: (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example I-291); 1-methyl-piperidin-4-ylamine (Example I-292); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example I-293); 4-pyrrolidin-1-yl-piperidine (Example I-294); N-methyl-piperazine (Example I-295); and 3,5-dimethyl-piperazine (Example I-296).

Examples I-297 to I-299

The compounds of Examples I-297 to I-299 were prepared following procedure 9.

Examples I-300 to I-661 were prepared according to the procedures referenced in the Tables herein. except as specifically described in the following paragraphs. When multiple procedures are referenced in the Tables separated by "/", the indicated procedures were performed sequentially.

Example I-311

3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

Example I-312

3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone was prepared following procedure 4 starting from 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid and 1-methyl-piperidin-4-ylamine.

Example I-330

4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Example I-331

4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide was prepared following procedure 4 starting from 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid and the corresponding amine.

Example I-342

3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

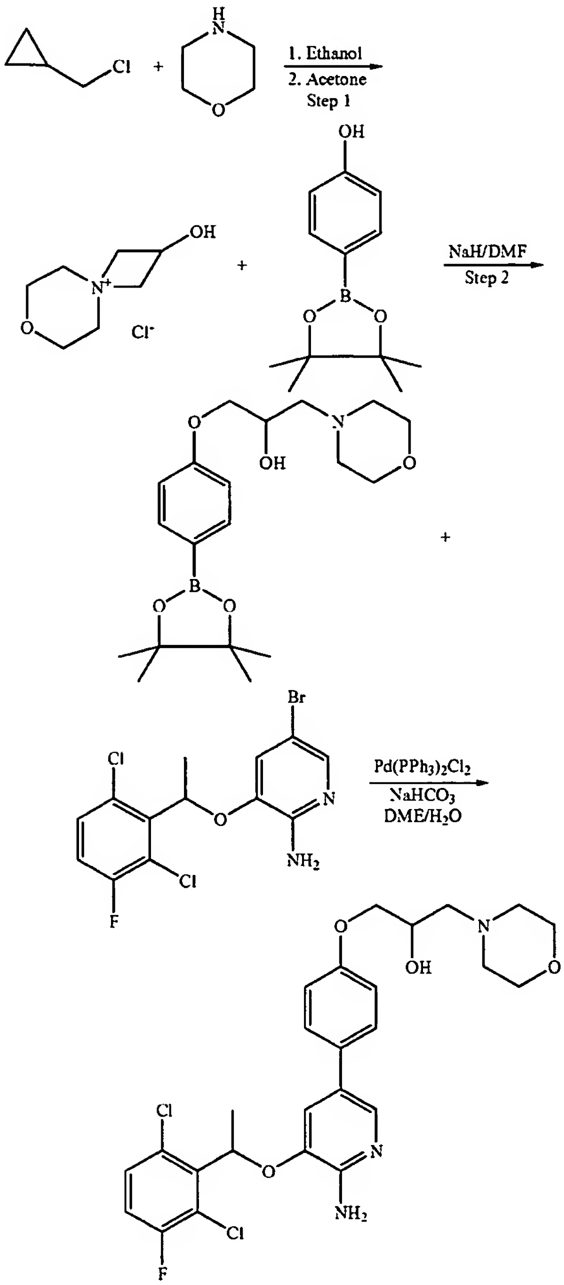
Example I-343

(3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone was prepared following procedure 4 starting from 3-(6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl)-benzoic acid and the corresponding amine.

Example I-359

1. Preparation of 2-hydroxy-7-oxa-4-azonia-spiro[3.5] nonane: To a solution of morpholine (17.4 mL, 0.2 mol, 1.0 eq.) in ethanol (20 mL) was added epichlorohydrin (16.1 ml, 1.03 eq.) from the addition funnel. The reaction was cooled with an ice water bath and gradually raised-to-room temperature. After 24 hr, the reaction was concentrated at 50° C. until no more distillate could be condensed. The resulting oil was stored at room temperature for 24–48 hr or until a significant mass of crystals was observed. The slurry was

diluted with acetone and filtered. The solids were dried under high vacuum. This provided 20 g of crystalline product. The mother liquors could be concentrated and the crystallization process repeated in increase recovery.



2. Preparation of 1-Morpholin-4-yl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propan-2-ol: 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (440 mg, 2 mmol) was added to a stirred suspension of NaH (96 mg, 2 eq) in DMF (10 mL) at 0° C. After 1 hr, 2-hydroxy-7-oxa-4-azonia-spiro[3.5]nonane (714 mg, 2 eq.) was added. The mixture was stirred at room temperature overnight. The reaction mixture was poured into sat'd NH_4Cl solution, and extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4 and

condensed to dryness. The crude product was purified with a silica gel column eluting with 2% methanol in methylene chloride to afford 220 mg of product as a pink solid (30%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (d, J=8.2 Hz, 2H), 6.915 (d, J=7.8 Hz, 2H), 4.89 (d, J=2.0 Hz, 1H), 3.98 (m, 3H), 3.55 (m, 4H), 2.40 (m, 6H), 1.27 (s, 12H). MS (m/e): 364 [M+H]+(100%).

3. 1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3yl}-phenoxy)-3-morpholin-4-yl-propan-2-ol was prepared following procedure 3 starting from 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine and 1-morpholin-4-yl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-propan-2-ol.

Example I-371

4-Methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide was prepared according to procedure 10.

Example I-386

3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

Example I-387

(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone was prepared following procedure 4 starting from 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid and 3,5-dimethyl-piperazine.

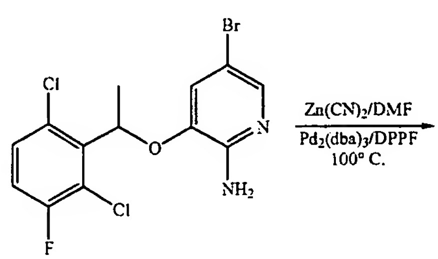
Example 399

4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl)-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridine-2-ylamine and 4-methoxycarbonylbenzeneboronic acid

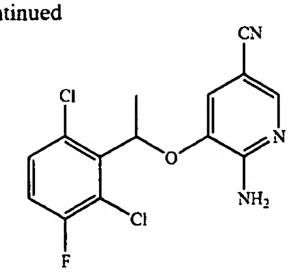
Example 400

4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide was prepared following procedure 4 starting from 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid and 2-pyrrolidin-1-yl-ethylamine.

Example I-454



-continued



To a solution of 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine (5.00 g, 13.15 mmol) in DMF (73 mL) and water (1 mL) was added $Zn(CN)_2$ (4.50 g, 26.3 mmol), $Pd_2(dba)_3$ (0.602 g, 0.65 mmol), and DPPF (0.86 g, 1.55 mmol). The mixture was degassed and charged with nitrogen for three time, and then stirred under nitrogen at 100° C. for 3 hr. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with a solution of sat. NH_4Cl-conc. NH_4OH-water (4:1:4), then dried over $MgSO_4$. The crude product was purified on a silica gel column eluting with ethyl acetate-hexanes (1:4) to provide 6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile as a white solide (4.15 g, 97% yield).

Example I-455

6-Amino-5-[1-(2,6-dichloro-3-cyano-phenyl)-ethoxy]-nicotinonitrile was obtained as a side product from the preparation of 6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile.

Example I-456

5-Aminomethyl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine was prepared with the reduction of 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile. To a solution of borane in THF (1.0 M, 16.8 mL, 16.8 mmol) was added 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]nicotinonitrile (785 mg, 2.41 mmol) in anhydrous THF (8 mL) at 0° C. under nitrogen. The reaction solution was stirred under nitrogen at 0° C. for 5 hr, and then HCl solution (6 N, 12 mL) was added slowly followed with the addition of water (12 mL) and methanol (80 mL). The mixture was stirred for overnight. After evaporation of solvents, the residue was partitioned between dichloromethane and NaOH solution (1 N). The water layer was extracted for three times, and the combined extracts were dried over $MgSO_4$. After filtration, evaporation and high vacuum dry, a white solid product was obtained (750 mg, 94% yield).

Example I-457

(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl)amide was prepared with the same procedure as Step 4 in procedure 11.

Example I-462

(S)-1-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)ethane-1,2-diol was prepared as follow: To a solution of asymmetic dihydroxylation-mix α (2.33 g) in a 1:1 mixture of t-BuOH and water (8 mL each) cooled to 0° C. was added 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine (500 mg, 1.67 mmol). The reaction mixture was stirred at 0° C. until consumption of the starting material. Three more loadings of AD-mix α was added periodically to increase the reaction rate. Water was added (5 mL) and the mixture was extracted with EtOAc (3x20 mL). The combined organic layer was dried over Na_2SO_4, and concentrated. The crude product was purified by reverse phase HPLC to provide (S)-1-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-ethane-1,2-diol (320 mg, 53% yield).

Example I-463

(R)-1-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-ethane-1,2-diol was prepared with the same procedure as Example I-462 with AD-mix α.

Examples II-1 to II-6

The compounds of Examples II-1 to II-6 were prepared according to the Suzuki coupling procedure 3 from 5-bromo-3-(2,6-dichloro-benzyloxy)-pyrazin-2-ylamine and: 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (Example II-1); 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]isothiazolidine 1,1-dioxide (Example II-2); 3-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (Example II-3); 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine (Example II-4); 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (Example II-5); and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Example II-6).

Example II-7

{4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl)[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared following the amidation procedure 4 from 4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-benzoic acid and (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine.

Example II-8

{4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone was prepared following the amidation procedure 4 from 4-[5-amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-benzoic acid and 4-pyrrolidin-1-yl-piperidine.

Examples II-9 to II-32

The compounds of Examples II-9 to II-32 were prepared following the Suzuki coupling procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine and the following compounds prepared according to the procedure in Example I-243: 2-morpholin-4-yl-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3.2]dioxaborolan-2-yl)-phenyl]-amide (Example II-9); 2-piperidin-1-yl-ethanesulfonic acid [4-(4.4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-10); 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-11); 2-pyrrolidin-1-yl-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example

II-12); 2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-13); 2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-14); 2-(cyclopropylmethyl-amino)-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-15); 2-dimethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-16); 2-diethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-17); 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-18); 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-19); 2-cyclopropylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-20); 2-[(3R)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-21); 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-22); 2-(4-acetyl-piperazin-1-yl)-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-23); 2-piperidin-1-yl-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-24); 2-diethylamino-ethanesulfonic acid [3-(4,4, 5,5-tetramethyl-[1, 3,2] dioxaborolan-2-yl)-phenyl]-amide (Example II-25); 2-morpholin-4-yl-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-26); 2-pyrrolidin-1-yl-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-27); 2-dimethylamino-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-28); 2-[4-(2-hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-29); 2-(cyclopropylmethyl-amino)-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-30); 2-[(3R)-3-hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-31); and 2-cyclopropylamino-ethanesulfonic acid [3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (Example II-32).

Example II-33

4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid was prepared following the Suzuki coupling procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxa-borolan-2-yl)-benzoic acid.

Example II-34

{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone was prepared following the amidation procedure 4 from 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid and (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine.

Examples II-35 to II-46

The compounds of Examples II-35 to II-46 were prepared according to the amidation procedure 4 from 4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid and: 2-pyrrolidin-1-yl-ethylamine (Example II-35); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-36); 1-[4-(2-amino-ethyl)-piperazin-1-yl]-ethanone (Example II-37); 3-pyrrolidin-1-yl-propylamine (Example II-38); (3S)-3-dimethylamino-pyrrolidine (Example II-39); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-40); 3,5-dimethyl-piperazine (Example II-41); 4-pyrrolidin-1-yl-piperidine (Example II-42); 3-morpholin-4-yl-propylamine (Example II-43); 1-methyl-piperidin-4-ylamine (Example II-44); 2-morpholin-4-yl-ethylamine (Example II-45); and N-methylpiperazine (Example II-46).

Example II-47

3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid was prepared following the Suzuki coupling procedure 3 from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine (Example II(b)) and 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Aldrich, Milwaukee).

Examples II-48 to II-60

The compounds of Examples II-48 to II-60 were prepared according to the amidation procedure 4 from 3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid and: N-methylpiperazine (Example II-48); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-49); (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-50); 3,5-dimethyl-piperazine (Example II-51); 3-morpholin-4-yl-propylamine (Example II-52); 4-pyrrolidin-1-yl-piperidine (Example II-53); (3S)-3-dimethylamino-pyrrolidine (Example II-54); 2-pyrrolidin-1-yl-ethyl amine (Example II-55); 1-methyl-piperidin-4-ylamine (Example II-56); (2S)-pyrrolidin-1-ylmethyl-pyrrolidine (Example II-57); 2-morpholin-4-yl-ethylamine (Example II-58); 2-(4-Acetyl-piperazin-1-yl)-ethylamine (Example II-59); and 3-pyrrolidin-1-yl-propylamine (Example II-60).

Example II-61

3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-y)-pyrazin-2-ylamine was prepared from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine and indole-5-boronic acid following procedure 3.

Examples II-62 to II-68

The compounds of Examples II-62 to II-68 were prepared according to procedure 5 from 3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyrazin-2-ylamine and: pyrrolidine (Example II-62); diethylamine (Example II-63); 1-piperazin-1-yl-ethanone (Example II-64); 2,6-dimethyl-morpholine (Example II-65); N—(S)-pyrrolidin-3-yl-acetamide (Example II-66); piperidine (Example II-67); and morpholine (Example II-68).

Example II-69

3-[1-(2-Chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine was prepared following the Suzuki coupling procedure 3 from 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-pyrazin-2-ylamine and 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine.

Example II-70

(3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine, compound with trifluoro-acetic acid, was prepared following the Suzuki coupling procedure 3 from 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-pyrazin-2-ylamine and 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine. The product was purified with a reversed phase C-18 preparative HPLC eluting with acetonitrile-water-trifluoroacetic acid and obtained as a trifluoroacetic acid salt.

Examples II-71 to II-83

The compounds of Examples II-71 to II-83 were prepared according to the Suzuki coupling procedure 3 from 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-ylamine and: 4-{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-ethyl}-morpholine, followed by purification with a reversed phase C-18 preparative HPLC eluting with acetonitrile-water-trifluoroacetic acid and obtained as a trifluoroacetic acid salt (Example II-71); N-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methane-sulfonamide (Example II-72); 2-pyrrolidin-1-yl-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-73); 2-(4-hydroxy-piperidin-1-yl)-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-74); 2-piperidin-1-yl-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared according to the procedure in Example I-243) (Example II-75); 2-(cyclopropylmethyl-amino)-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-76); 2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-77); 2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-78); 2-dimethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-79); 2-morpholin-4-yl-ethanesulfonic acid (4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-80); 2-diethylamino-ethanesulfonic acid [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243) (Example II-81); 2-cyclopropylamino-ethanesulfonic acid (4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-amide (prepared as in Example I-243); and 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Example II-83).

Examples II-84 to II-88

The compounds of Examples II-84 to II-88 were prepared according to the amidation procedure 4 from 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}benzoic acid and: (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-84); (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester, followed by de-protection of Boc-group with trifluoroacetic acid in dichloromethane (Example II-85); (2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine (Example II-86); 2-(4-acetyl-piperazin-1-yl)-ethylamine (Example II-87); and (2S)-pyrrolidin-1-ylmethyl-pyrrolidine (Example II-88).

Example II-89

3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid was prepared following the Suzuki coupling procedure 3 from 5-bromo-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-ylamine and 3-(4, 4, 5, 5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid.

Example II-90

3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide was prepared following the amidation procedure-4- from 3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 1-methyl-piperidin-4-ylamine.

Example II-91

3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide was prepared following the amidation procedure 4 from 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 3-pyrrolidin-1-yl-propylamine.

Example II-92

(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone was prepared following the amidation procedure 4 from 3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 4-pyrrolidin-1-yl-piperidin-1-ylamine.

Example II-93

4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid was prepared following the Suzuki coupling procedure 3 from 5-bromo-3(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-ylamine and 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid.

Example II-94

4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide was prepared following the amidation procedure 4 from 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid and 2-morpholin-4-yl-ethylamine.

Example II-95

4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide was prepared following the amidation procedure 4 from 4-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid and 1-methyl-piperidin-4-ylamine.

Examples II-96 to II-211 were prepared according to the procedures referenced in the Tables herein, except as specifically described in the following paragraphs.

Example II-108

4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl)-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Example II-109

4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide was prepared following procedure 4 starting from 4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 3-pyrrolidin-1-yl-propylamine.

Example II-121

3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid using the same procedures a 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

Example II-122

{3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone was prepared following procedure 4 starting from 3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid and 4-pyrrolidin-1-yl-piperidin-1-ylamine.

Example II-145

4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy)-pyrazin-2-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Example II-148

4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide was prepared following procedure 4 starting from 4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and (R)-2-hydroxy-3-pyrrolidin-1-yl-propylamine.

Example II-156

4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-ylamine and 4-methoxycarbonylbenzeneboronic acid.

Example II-157

(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone was prepared following procedure 4 starting from 4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 4-pyrrolidin-1-yl-piperidin-1-ylamine.

Example II-168

3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid was prepared using the same procedure as 4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid from 5-bromo-3-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-ylamine and 3-methoxycarbonylbenzeneboronic acid.

Example II-169

3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy)-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide was prepared following procedure 4 starting from 3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid and 1-methyl-piperidin-4-ylamine.

Example II-193

5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid was prepared following procedure 3 starting from 5-bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine and 5-carboxythiophene-2-boronic acid.

Example II-194

{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone was prepared following procedure 4 starting from 5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid and 4-methyl-piperazin-1-ylamine.

Examples L-1 to L-176 were prepared according to procedure 40. In Table 5, the compounds are grouped into sections, with each section having a letter designation. Example numbers are assigned left to right by rows. For example, in Section A, the compounds in the top row, from left to right, are Examples L-1 to L-4, and the compounds in the second row are, from left to right, Examples L-5-L-8. % Inhibition is the percent c-MET inhibition at 50 nM.

Examples L-177 to L-352 were prepared according to procedure 41. In Table 6, the compounds are grouped into sections, with each section having a letter designation. Example numbers are assigned left to right by rows. % Inhibition is the percent c-MET inhibition at 1 μM.

Examples L-353 to L-548 were prepared according to procedure 42. In Table 7, the compounds are grouped into sections, with each section having a letter designation.

Example numbers are assigned left to right by rows. % Inhibition is the percent c-MET inhibition at 1 μM.

Examples L-549 to L-636 were prepared according to procedure 43. In Table 8, the compounds are grouped into sections, with each section having a letter designation. Example numbers are assigned left to right by rows. % Inhibition is the percent c-MET inhibition at 1 μM.

BIOLOGICAL EXAMPLES

It will be appreciated that, in any given series of compounds, a range of biological activities will be observed. In its presently preferred aspects, this invention relates to novel compounds capable of modulating, regulating and/or inhibiting protein kinase activity. The following assays may be employed to select those compounds demonstrating the optimal degree of the desired activity.

Assay Procedures

The following in vitro assay may be used to determine the level of activity and effect of the different compounds of the present invention on one or more of the PKs. Similar assays can be designed along the same lines for any PK using techniques well known in the art. A literature reference is provided (Technikova-Dobrova Z, Sardanelli A M, Papa S FEBS Lett. 1991 Nov. 4; 292: 69–72).

The general procedure is as follows: compounds and kinase assay reagents are introduced into test wells. The assay is initiated by addition of the kinase enzyme. Enzyme inhibitors reduce the measured activity of the enzyme.

In the continuous-coupled spectrophotometric assay the time-dependent production of ADP by the kinase is determined by analysis of the rate of consumption of NADH by measurement of the decrease in absorbance at 340 nm. As the PK produces ADP it is re-converted to ATP by reaction with phosphoenol pyruvate and pyruvate kinase. Pyruvate is also produced in this reaction. Pyruvate is subsequently converted to lactate by reaction with lactate dehydrogenase, which simultaneously converts NADH to NAD. NADH has a measurable absorbance at 340 nm whereas NAD does not.

The presently preferred protocol for conducting the continuous-coupled spectrophotometric experiments for specific PKs is provided below. However, adaptation of this protocol for determining the activity of compounds against other RTKs, as well as for CTKs and STKs, is well within the scope of knowledge of those skilled in the art.

HGFR Continuous-coupled Spectrophotometric Assay

This assay analyzes the tyrosine kinase activity of HGFR on the Met-2 substrate peptide, a peptide derived from the activation loop of the HGFR.

Materials and Reagents:

1. HGF enzyme from Upstate (Met, active) Cat. #14-526
2. Met-2 Peptide (HGF Activation Loop) Ac-ARDMYDKEYYSVHNK (MW=1960). Dissolve up in 200 mM HEPES, pH 7.5 at 10 mM stock.
3. 1 M PEP (phospho-enol-pyruvate) in 200 mM HEPES, pH 7.5.
4. 100 mM NADH (B-Nicotinamide Adenine Dinucleotide, Reduced Form) in 200 mM HEPES, pH 7.5
5. 4 M $MgCl_2$ (Magnesium Chloride) in ddH_2O
6. 1 M DTT (Dithiothreitol) in 200 mM HEPES, pH 7.5
7. 15 Units/mL LDH (Lactic Dehydrogenase)
8. 15 Units/mL PK (Pyruvate Kinase)
9. 5 M NaCl dissolved in ddH_2O
10. Tween-20 (Protein Grade) 10% Solution
11. 1 M HEPES buffer: (N-[2-Hydroxethyl]piperazine-N-[2-ethanesulfonic acid]) Sodium Salt. Dissolve in ddH_2O, adjust pH to 7.5, bring volume to 1 L. Filter at 0.1 μm.
12. HPLC Grade Water; Burdick and Jackson #365-4, 1×4 liters (or equivalent)
13. 100% DMSO (SIGMA)
14. Costar #3880—black clear flat bottom half area plates for K_i determination and % inhibition
15. Costar #3359—96 well polypropylene plates, round bottom for serial dilutions
16. Costar #3635—UV-plate clear flat bottom plates for % inhibition
17. Beckman DU-650 w/micro cell holders
18. Beckman 4-position micro cell cuvette

Procedure:

Prep Dilution Buffer (DB) for Enzyme (For 30 mL prep)

1. DB final concentration is 2 mM DTT, 25 mM $NaCl_2$, 5 mM $MgCl_2$, 0.01% Tween-20, and 50 mM HEPES buffer, pH 7.5.
2. Make up 50 mM HEPES by adding 1.5 mL 1 M HEPES into 28.1 mL of ddH_2O. Add rest of the reagents. Into 50 mL conical vial, add 60 uL of 1 M DTT, 150 uL 5 M $NaCl_2$, 150 uL 1 M $MgCl_2$, and 30 uL of 10% Tween-20 to give total volume of 30 mL.
3. Vortex for 5–10 seconds
4. Aliquot out DB at 1 mL/tube and label tubes as "DB HGFR"
5. Note: This can be prepared and stored ahead of time.
6. Freeze un-used aliquots in microcentrifuge tubes at −20° C. freezer.

Prep Compounds

1. For compound dilution plate, add 4 uL of 10 mM stock into column 1 of plate, and bring volume to 100 uL with 100% DMSO.
2. Set up the Precision 2000 dilution method. A final concentration of 200 uM compound in 50% DMSO, 100 mM HEPES (1:2 serial dilution).

Prep Coupled Enzymatic Buffer:

1. Final concentration in assay:
   Reagent (Stock Conc.) Final Conc. In Assay
   a. PEP (1 M) 1 mM
   b. NADH (100 mM) 300 uM
   c. $MgCl_2$ (4 M) 20 mM
   d. DTT(1 M) 2 mM
   e. ATP (500 mM) 300 uM
   f. HEPES 200 mM (pH 7.5) 100 mM
   g. Pyruvate Kinase (PK) 15 units/mL
   h. Lactic Dehydrogenase (LDH) 15 units/mL
   i. Met-2 peptide (10 mM) 0.500 mM
   j. HGFR 50 nM
2. For a 10 mL reaction buffer add 10 uL of 1 M PEP, 33 uL of 100 mM NADH, 50 uL of 4 M $MgCl_2$, 20 uL of 1 M DTT, 6 uL of 500 mM ATP, and 500 uL of 10 mM Met-2 peptide into 100 mM HEPES buffer pH 7.5 and vortex/mix.
3. Add coupling enzymes, LDH and PK, into reaction mix. Mix by gentle inversion.

Running Samples

1. Spectrophotometer settings:

i.	Absorbance wavelength (λ):	340 nm
ii.	Incubation time:	10 min

-continued

iii.	Run time:	10 min
iv.	Temperature:	37° C.

2. Add 85 μL of CE reaction mix into each well of assay plate.
3. Add 5 μL of diluted compound into a well of the assay plate.
4. Add 5 μL of 50% DMSO for negative control into last column of assay plate.
5. Mix with multi-channel pipettor or orbital shaker.
6. Pre-incubate for 10 minutes at 37° C.
7. Add 10 μL of 500 nM HGFR to each well of assay plate; the final HGFR concentration is 50 nM in a total final volume of 100 μL.
8. Measure activity for 10 minutes at λ=340 nm and 37° C.

The following in vitro assays may be used to determine the level of activity and effect of the different compounds of the present invention on one or more of the PKs. Similar assays can be designed along the same lines for any PK using techniques well known in the art.

Several of the assays described herein are performed in an ELISA (Enzyme-Linked Immunosorbent Sandwich Assay) format (Voller, et al., 1980, "Enzyme-Linked Immunosorbent Assay," Manual of Clinical Immunology, 2d ed., Rose and Friedman, Am. Soc. Of Microbiology, Washington, D.C., pp. 359–371). General procedure is as follows: a compound is introduced to cells expressing the test kinase, either naturally or recombinantly, for a selected period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added. The cells are lysed and the lysate is transferred to the wells of an ELISA plate previously coated with a specific antibody recognizing the substrate of the enzymatic phosphorylation reaction. Non-substrate components of the cell lysate are washed away and the amount of phosphorylation on the substrate is detected with an antibody specifically recognizing phosphotyrosine compared with control cells that were not contacted with a test compound.

The presently preferred protocols for conducting the ELISA experiments for specific PKs is provided below. However, adaptation of these protocols for determining the activity of compounds against other RTKs, as well as for CTKs and STKs, is well within the scope of knowledge of those skilled in the art.

Other assays described herein measure the amount of DNA made in response to activation of a test kinase, which is a general measure of a proliferative response. General procedure for this assay is as follows: a compound is introduced to cells expressing the test kinase, either naturally or recombinantly, for a selected period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added. After incubation at least overnight, a DNA labeling reagent such as 5-bromodeoxyuridine (BrdU) or H^3-thymidine is added. The amount of labeled DNA is detected with either an anti-BrdU antibody or by measuring radioactivity and is compared to control cells not contacted with a test compound.

MET Transphosphorylation Assay

This assay is used to measure phosphotyrosine levels on a poly(glutamic acid:tyrosine, 4:1) substrate as a means for identifying agonists/antagonists of met transphosphorylation of the substrate.

Materials and Reagents:

1. Corning 96-well ELISA plates, Corning Catalog #25805-96.
2. Poly(glu-tyr), 4:1, Sigma, Cat. No; P 0275.
3. PBS, Gibco Catalog #450-1300EB
4. 50 mM HEPES
5. Blocking Buffer: Dissolve 25 g Bovine Serum Albumin, Sigma Cat. No A-7888, in 500 mL PBS, filter through a 4 μm filter.
6. Purified GST fusion protein containing the Met kinase domain, SUGEN, Inc.
7. TBST Buffer.
8. 10% aqueous (MilliQue H_2O) DMSO.
9. 10 mM aqueous (dH_2O) Adenosine-5'-triphosphate, Sigma Cat. No. A-5394.
10. 2× Kinase Dilution Buffer: for 100 mL, mix 10 mL 1 M HEPESat pH 7.5 with 0.4 mL 5% BSA/PBS, 0.2 mL 0.1 M sodium orthovanadate and 1 mL 5 M sodium chloride in 88.4 mL dH_2O.
11. 4× ATP Reaction Mixture: for 10 mL, mix 0.4 mL 1 M manganese chloride and 0.02 mL 0.1 M ATP in 9.56 mL dH_2O.
12. 4× Negative Controls Mixture: for 10 mL, mix 0.4 mL 1 M manganese chloride in 9.6 mL dH_2O.
13. NUNC 96-well V bottom polypropylene plates, Applied Scientific Catalog # S-72092
14. 500 mM EDTA.
15. Antibody Dilution Buffer: for 100 mL, mix 10 mL 5% BSA/PBS, 0.5 mL 5% Carnation® Instant Milk in PBS and 0.1 mL 0.1 M sodium orthovanadate in 88.4 mL TBST.
16. Rabbit polyclonal antophosphotyrosine antibody, SUGEN, Inc.
17. Goat anti-rabbit horseradish peroxidase conjugated antibody, Biosource, Inc.
18. ABTS Solution: for 1 L, mix 19.21 g citric acid, 35.49 g Na_2HPO_4 and 500 mg ABTS with sufficient dH_2O to make 1 L.
19. ABTS/H_2O_2: mix 15 mL ABST solution with 2μL H_2O_2 five minutes before use.
20. 0.2 M HCl

Procedure:

1. Coat ELISA plates with 2 μg Poly(Glu-Tyr) in 100 μL PBS, hold-overnight at 4° C.
2. Block plate with 150 μL of 5% BSA/PBS for 60 min.
3. Wash plate twice with PBS then once with 50 mM Hepes buffer pH 7.4.
4. Add 50 μl of the diluted kinase to all wells. (Purified kinase is diluted with Kinase Dilution Buffer. Final concentration should be 10 ng/well.)
5. Add 25 μL of the test compound (in 4% DMSO) or DMSO alone (4% in dH_2O) for controls to plate.
6. Incubate the kinase/compound mixture for 15 minutes.
7. Add 25 μL of 40 mM $MnCl_2$ to the negative control wells.
8. Add 25 μL ATP/$MnCl_2$ mixture to the all other wells (except the negative controls). Incubate for 5 min.
9. Add 25 μL 500 mM EDTA to stop reaction.
10. Wash plate 3× with TBST.
11. Add 100 μL rabbit polyclonal anti-Ptyr diluted 1:10,000 in Antibody Dilution Buffer to each well. Incubate, with shaking, at room temperature for one hour.
12. Wash plate 3× with TBST.
13. Dilute Biosource HRP conjugated anti-rabbit antibody 1:6,000 in Antibody Dilution buffer. Add 100 μL per well and incubate at room temperature, with shaking, for one hour.

14. Wash plate 1× with PBS.

15. Add 100 μl of $ABTS/H_2O_2$ solution to each well.

16. If necessary, stop the development reaction with the addition of 100 μl of 0.2 M HCl per well.

17. Read plate on Dynatech MR7000 ELISA reader with the test filter at 410 nM and the reference filter at 630 nM.

BrdU Incorporation Assays

The following assays use cells engineered to express a selected receptor and then evaluate the effect of a compound of interest on the activity of ligand-induced DNA synthesis by determining BrdU incorporation into the DNA.

The following materials, reagents and procedure are general to each of the following BrdU incorporation assays. Variances in specific assays are noted.

General Materials and Reagents:

1. The appropriate ligand.

2. The appropriate engineered cells.

3. BrdU Labeling Reagent: 10 mM, in PBS, pH7.4 (Roche Molecular Biochemicals, Indianapolis, Ind.).

4. FixDenat: fixation solution (Roche Molecular Biochemicals, Indianapolis, Ind.).

5. Anti-BrdU-POD: mouse monoclonal antibody conjugated with peroxidase (Chemicon, Temecula, Calif.).

6. TMB Substrate Solution: tetramethylbenzidine (TMB, ready to use, Roche Molecular Biochemicals, Indianapolis, Ind.).

7. PBS Washing Solution: 1×PBS, pH 7.4.

8. Albumin, Bovine (BSA), fraction V powder (Sigma Chemical Co., USA).

General Procedure:

1. Cells are seeded at 8000 cells/well in 10% CS, 2 mM Gln in DMEM, in a 96 well plate. Cells are incubated overnight at 37° C. in 5% CO_2.

2. After 24 hours, the cells are washed with PBS, and then are serum-starved in serum free medium (0% CS DMEM with 0.1% BSA) for 24 hours.

3. On day 3, the appropriate ligand and the test compound are added to the cells simultaneously. The negative control wells receive serum free DMEM with 0.1% BSA only; the positive control cells receive the ligand but no test compound. Test compounds are prepared in serum free DMEM with ligand in a 96 well plate, and serially diluted for 7 test concentrations.

4. After 18 hours of ligand activation, diluted BrdU labeling reagent (1:100 in DMEM, 0.1% BSA) is added and the cells are incubated with BrdU (final concentration is 10 μM) for 1.5 hours.

5. After incubation with labeling reagent, the medium is removed by decanting and tapping the inverted plate on a paper towel. FixDenat solution is added (50 μl/well) arid the plates are incubated at room temperature for 45 minutes on a plate shaker.

6. The FixDenat solution is removed by decanting and tapping the inverted plate on a paper towel. Milk is added (5% dehydrated milk in PBS, 200 μl/well) as a blocking solution and the plate is incubated for 30 minutes at room temperature on a plate shaker.

7. The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution is added (1:200 dilution in PBS, 1% BSA, 50 μl/well) and the plate is incubated for 90 minutes at room temperature on a plate shaker.

8. The antibody conjugate is removed by decanting and rinsing the wells 5 times with PBS, and the plate is dried by inverting and tapping on a paper towel.

9. TMB substrate solution is added (100 μl/well) and incubated for 20 minutes at room temperature on a plate shaker until color development is sufficient for photometric detection.

10. The absorbance of the samples are measured at 410 nm (in "dual wavelength" mode with a filter reading at 490 nm, as a reference wavelength) on a Dynatech ELISA plate reader.

HGF-Induced BrdU Incorporation Assay

Materials and Reagents:

1. Recombinant human HGF (Cat. No. 249-HG, R&D Systems, Inc. USA).

2. BxPC-3 cells (ATCC CRL-1687).

Remaining Materials and Reagents, as above.

Procedure:

1. Cells are seeded at 9000 cells/well in RPMI 10% FBS in a 96 well plate. Cells are incubated overnight at 37° C. in 5% CO_2.

2. After 24 hours, the cells are washed with PBS, and then are serum starved in 100 μL serum-free medium (RPMI with 0.1% BSA) for 24 hours.

3. On day 3, 25 μL containing ligand (prepared at 1 μg/mL in RPMI with 0.1% BSA; final HGF conc. is 200 ng/mL) and test compounds are added to the cells. The negative control wells receive 25 μL serum-free RPMI with 0.1% BSA only; the positive control cells receive the ligand (HGF) but no test compound. Test compounds are prepared at 5 times their final concentration in serum-free RPMI with ligand in a 96 well plate, and serially diluted to give 7 test concentrations. Typically, the highest final concentration of test compound is 100 μM, and 1:3 dilutions are used (i.e. final test compound concentration range is 0.137–100 μM).

4. After 18 hours of ligand activation, 12.5 μL of diluted BrdU labeling reagent (1:100 in RPMI, 0.1% BSA) is added to each well and the cells are incubated with BrdU (final concentration is 10 μM) for 1 hour.

5. Same as General Procedure.

6. Same as General Procedure.

7. The blocking solution is removed by decanting and the wells are washed once with PBS. Anti-BrdU-POD solution (1:100 dilution in PBS, 1% BSA) is added (100 μL/well) and the plate is incubated for 90 minutes at room temperature on a plate shaker.

8. Same as General Procedure.

9. Same as General Procedure.

10. Same as General Procedure.

In Vivo Animal Models

Xenograft Animal Models

The ability of human tumors to grow as xenografts in athymic mice (e.g. Balb/c, nu/nu) provides a useful in vivo model for studying the biological response to therapies for human tumors. Since the first successful xenotransplantation of human tumors into athymic mice, (Rygaard and Povisen, 1969, Acta Pathol. Microbial. Scand. 77:758–760), many different human tumor cell lines (e.g., mammary, lung, genitourinary, gastro-intestinal, head and neck, glioblastoma, bone, and malignant melanomas) have been transplanted and successfully grown in nude mice. The following assays may be used to determine the level of activity, specificity and effect of the different compounds of the present invention. Three general types of assays are useful for evaluating compounds: cellular/catalytic, cellular/biological and in vivo. The object of the cellular/catalytic assays is to determine the effect of a compound on the ability

of a TK to phosphorylate tyrosines on a known substrate in a cell. The object of the cellular/biological assays is to determine the effect of a compound on the biological response stimulated by a TK in a cell. The object of the in vivo assays is to determine the effect of a compound in an animal model of a particular disorder such as cancer.

Suitable cell lines for subcutaneous xenograft experiments include C6 cells (glioma, ATCC # CCL 107), A375 cells (melanoma, ATCC # C.RL 1619), A431 cells (epidermoid carcinoma, ATCC # C.RL 1555), Calu 6 cells (lung, ATCC # HTB 56), PC3 cells (prostate, ATCC # C.RL 1435), SKOV3TP5 cells, S114 (NIH3T3 fibroblast cell line genetically engineered for cMet and HGF expressions from NCI), U-87 MG (human malignant glioma, ATCC HTB 14) and NIH 3T3 fibroblasts genetically engineered to overexpress EGFR, PDGFR, IGF-1R or any other test kinase. The following protocol can be used to perform xenograft experiments:

Female athymic mice (BALB/c, nu/nu) are obtained from Simonsen Laboratories (Gilroy, Calif.). All animals are maintained under clean-room conditions in Micro-isolator cages with Alpha-dri bedding. They receive sterile rodent chow and water ad libitum.

Cell lines are grown in appropriate medium (for example, MEM, DMEM, Ham's F10, or Ham's F12 plus 5%–10% fetal bovine serum (FBS) and 2 mM glutamine (GLN)). All cell culture media, glutamine, and fetal bovine serum are purchased from Gibco Life Technologies (Grand Island, N.Y.) unless otherwise specified. All cells are grown in a humid atmosphere of 90–95% air and 5–10% CO_2 at 37° C. All cell lines are routinely subcultured twice a week and are negative for mycoplasma as determined by the Mycotect method (Gibco).

Cells are harvested at or near confluency with 0.05% Trypsin-EDTA and pelleted at 450×g for 10 min. Pellets are resuspended in sterile PBS or media (without FBS) to a particular concentration and the cells are implanted into the hindflank of the mice (8–10 mice per group, $2–10\times10^6$ cells/animal). Tumor growth is measured over 3 to 6 weeks using venier calipers. Tumor volumes are calculated as a product of length×width×height unless otherwise indicated. P values are calculated using the Students t-test. Test compounds in 50–100 µL excipient (DMSO, or VPD:D5W) can be delivered by IP injection at different concentrations generally starting at day one after implantation.

Met Phosohorylation—Cellular Assay

Materials and Reagents:

1. Falcon 10 cm culture dishes.
2. A549 lung carcinoma cells.
3. F12K growth medium (with 2% FBS+2 mM glutamine.
4. F12K assay medium (with 0.1% BSA).
5. Fisher cell scrapers.
6. Lysis buffer (HNTG, 1 mM sodium orthovanidate, 1 mM PMSF and 2 mM sodium fluoride).
7. 1.5 mL Eppendorf tubes.
8. Eppendorf microcentrifuge.
9. BCA assay reagents A and B (#23223 and 23224, Pierce).
10. Sample tube rotator.
11. Gel blot container rotator.
12. 5× sample buffer.
13. Novex pre-cast tris-glycine 8% acrylamide gels.
14. Bio-Rad electrophoresis chamber.
15. SDS-PAGE buffer.
16. TBS (pH 7.6)+0.1% Triton X-100 (TBST), with and without 5% milk.
17. Western blot transfer buffer.
18. Osmonics nitrocellulose paper.
19. Bio-Rad Transblot paper.
20. Gel transfer apparatus.
21. Anti-phosphotyrosine (mouse monoclonal).
22. Bio-Rad Kaleidoscope Prestained Standards (161-0324).
23. Anti-h-met (C-28) rabbit polyclonal, conjugated and non-conjugated with agarose (#sc-161 AC and sc-161, Santa Cruz Biotechnology, Inc.).
24. Donkey and anti-rabbit Ig-HRP (NA 934, Amersham).
25. Sheet anti-mouselg-HRP (NA 931, Amersham).
26. SuperSignal West Pico Chemiluminescent Substrate (#34080, Pierce).
27. Saran Wrap.
28. Kodak BioMax exposure cassette.
29. Fuji X-ray film.
30. Kodak film developer.

Procedure:

1. Plate cells in 10 cm dishes with growth medium with 2% FBS+2 mM glutamine. Grow to near confluency.
2. Serum starve cells overnight in assay medium with 0.1% BSA.
3. Add drug to the plates, one dose per plate, usually in a 2-flod titration. Add assay medium (with the same DMSO concentration as the drugs) for no drug.
4. Incubate plates 4–5 hours with the drug, then add HG, 50 ng/mL for 10 minutes.
5. Wash plates once with PBS, add 400 µl lysis buffer, and scrape off the cells. Collect in 1.5 mL Eppendorf tubes.
6. After about 10–20 minutes in the lysis buffer, centrifuge lysates in a microcentrifuger at full speed (14,000 g) and collect the supernatants in a separate Eppendorf tube.
7. Determine protein concentration with the BCA assay reagents.
8. Adjust sample concentration to 0.5 mg protein in 0.4 mL using lysis buffer.
9. Add 15 µl anti-h-met AC for immunoprecipitation, rotate samples for 2 hours at 4° C.
10. Wash samples 3 times with lysis buffer and resuspend in 35 µl 5× sample buffer.
11. Boil sample at 100° C. for 10 minutes and microcentrifuge at highest setting for 30 minutes to pellet the agarose beads.
12. Load 15 µl each to 2 gels, one for anti-phosphorylation and the other for anti-h-met. Also load 10 µl of prestained standards, one lane per gel.
13. Run gel around 100–125 V, then transfer gel to nitrocellulose either overnight at 70 mAmps or 1 hour at 500 mAmps.
14. Block membranes on rotator for 1 hour in TBS+0.1% Triton X-100 (TBST)+5% PBS. All steps from this point are at room temperature unless otherwise unless otherwise noted.
15. Add 0.8 µg/mL antiphosphotyrosine and 0.25 µg/mL anti-h-met on rotator either for 2 hours or overnight.
16. Wash membranes 3 times 5 minutes each in TBST on rotator.
17. Add HRP-conjugated antibodies sheep anti-mouse for the antiphosphotyroeins; donkey anti-rabbit for the nati-h-met) at 1:5000 for approximately 45 minutes on rotator.

18. Wash membranes 3 times for 5 minutes each in TBST on rotator.

19. Add the 2 reagents in the SuperSignal kit together in equal-volumes (3 mL+3 mL for each blot), rotate for 1–2 minutes.

20. Wrap blots in Saran Wrap and tape securely inside the exposure cassette.

21. In the darkroom with only the safety light on, place a sheet of film inside the cassette. After an allotted time, remove film and place in the developer machine for automatic processing. Experiment with the exposure time to get proper exposure.

TABLES

TABLE 1

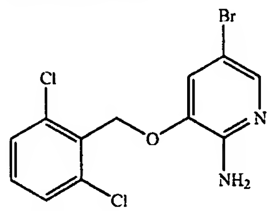
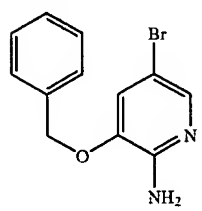
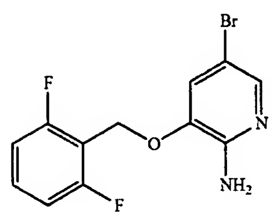
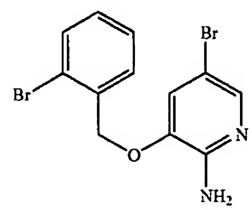
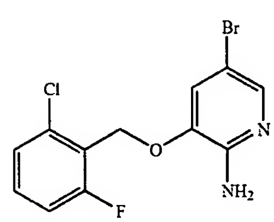
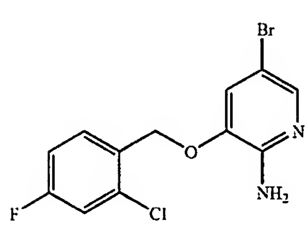
No.	Structure	Name	Met IC_{50} (μM)	^{1}H-NMR	MS m/z (M + 1)
I(a)		5-Bromo-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	5.3	(400 MHz, DMSO-d_6) δ 7.62 (m, 1H), 7.56(m, 2H), 7.46(m, 2H), 5.80(s, 2H), 5.22(s, 2H)	349
I(b)		3-Benzyloxy-5-bromo-pyridin-2-ylamine	>20	(400 MHz, DMSO-d_6) δ 7.56(d, J=2 Hz, 1H), 7.47(d, J=7.2 Hz, 2H), 7.38(m, 2H), 7.32(d, J=7.2 Hz, 1H), 7.26(d, J=2 Hz, 1H), 5.95(s, 2H), 5.14(s, 2H)	280
I(c)		5-Bromo-3-(2,6-difluoro-benzyloxy)-pyridin-2-ylamine	40% at 20 μM	(400 MHz, DMSO-d_6) δ 7.60(d, 1H), 7.52(m, 1H), 7.40(d, 1H), 7.18(m, 2H), 5.81(br. S. 2H), 5.12(s, 2H)	315 (M+)
I(d)		5-Bromo-3-(2-bromo-benzyloxy)-pyridin-2-ylamine	>20	(400 MHz, DMSO-d_6) δ 7.65 (m, 2H), 7.60(d, 1H), 7.42(m, 2H), 7.30(d, 1H), 5.94(s 2H), 5.13 (s, 2H)	357(M+)
I(e)		5-Bromo-3-(2-chloro-6-fluoro-benzyloxy)-pyridin-2-ylamine	>20	(400 MHz, DMSO-d_6) δ 7.80–7.30(m, 5H), 5.80(br s, 2H), 5.15(s, 2H)	331
I(f)		5-Bromo-3-(2-chloro-4-fluoro-benzyloxy)-pyridin-2-ylamine		(400 MHz, DMSO-d_6) δ 7.80–7.20(m, 5H), 5.95(br s, 2H), 5.10(s, 2H)	331

TABLE 1-continued

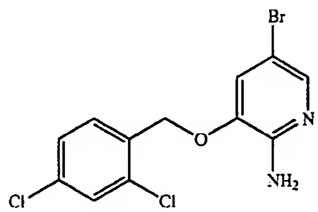
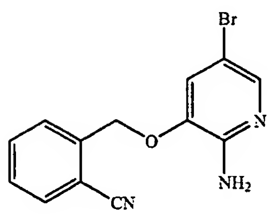
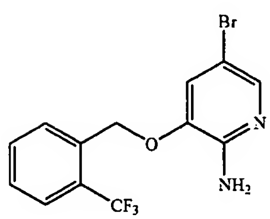
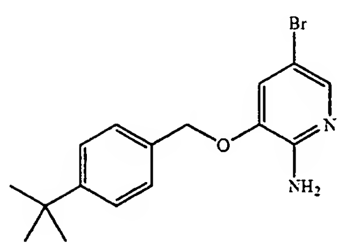
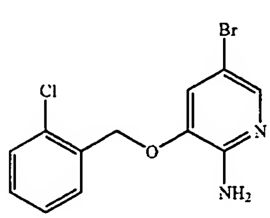
No.	Structure	Name	Met IC_{50} (μM)	^{1}H-NMR	MS m/z (M + 1)
I(g)		5-Bromo-3-(2,4-dichloro-benzyloxy)-pyridin-2-ylamine		(400 MHz, DMSO-d_6) δ 7.80–7.50(m, 5H), 6.20(br s, 2H), 5.20(s, 2H)	348
I(h)		2-(2-Amino-5-bromo-pyridin-3-yloxymethyl)-benzonitrile		(400 MHz, DMSO-d_6) δ 7.90–7.30(m, 6H), 5.90(br s, 2H), 5.20(s, 2H)	304 (M+)
I(i)		5-Bromo-3-(2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine		(400 MHz, DMSO-d_6) δ 7.80–7.30(m, 6H), 6.00(br s, 2H), 5.25(s, 2H)	347
I(j)		5-Bromo-3-(4-tert-butyl-benzyloxy)-pyridin-2-ylamine		(400 MHz, DMSO-d_6) δ 7.50–7.20(m, 6H), 5.85(br s, 2H), 5.05(s, 2H), 1.25(s, 9H)	335 (M+)
I(k)		5-Bromo-3-(2-chloro-benzyloxy)-pyridin-2-ylamine		(400 MHz, DMSO-d_6) δ 7.70–7.20(m, 6H), 5.90(br s, 2H), 5.15(s, 2H)	313

TABLE 1-continued

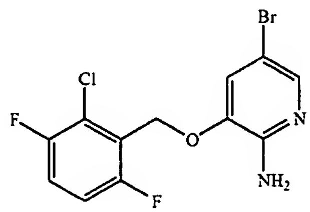
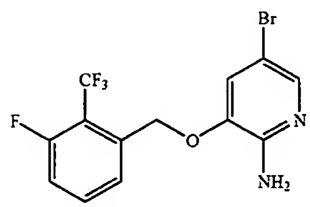
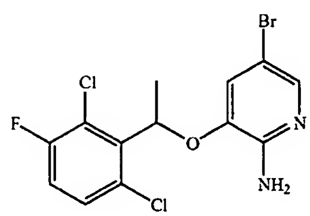
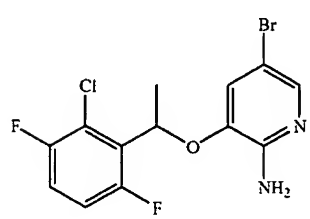
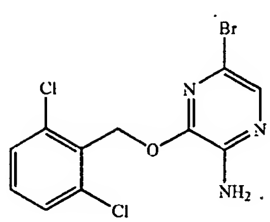
No.	Structure	Name	Met IC_{50} (μM)	^1H-NMR	MS m/z (M + 1)
I(l)		5-Bromo-3-(2-chloro-3.6-difluoro-benzyloxy)-pyridin-2-ylamine	5.3	($CDCl_3$, 300 MHz) δ 4.7–4.8 (brs, 2H), 5.21(s, 2H), 7.03–7.10(dt, 1H, J, 4.1, 9.1), 7.17–7.25(m, 2H), 7.75–7.76(d, J, 1.86).	
I(m)		5-Bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-2-ylamine			365
I(n)		5-Bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		($CDCl_3$, 300 MHz) δ 1.85–1.95 (d, 3H), 4.7–5.0(brs, 2H), 5.9–6.01(q, 1H), 6.8–6.95(d, 1H), 7.01–7.2(t, 1H), 7.4–7.45(m, 1H), 7.8–7.85(d, 1H).	
I(o)		5-Bromo-3-[1-(2-chloro-3.6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine			364
II(a)		5-Bromo-3-(2.6-dichloro-benzyloxy)-pyrazin-2-ylamine	>20	(400 MHz, DMSO-d_6) δ 5.45(s, 2H), 6.45(s, 2H), 7.50(m, 3H), 7.63(s, 1H)	350

TABLE 1-continued

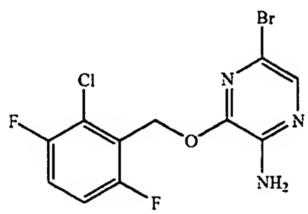
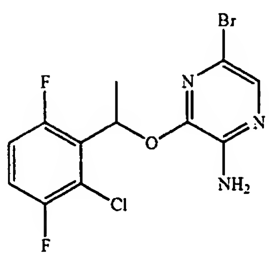
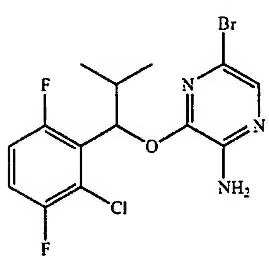
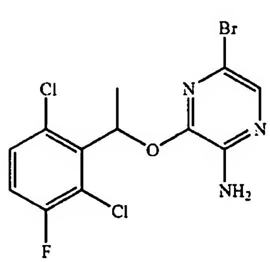
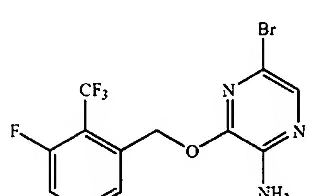
No.	Structure	Name	Met IC_{50} (μM)	^1H-NMR	MS m/z (M + 1)
II(b)		5-Bromo-3-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-ylamine	>20	(300 MHz, $CDCl_3$) δ 7.7(s, 1H), 7.23–7.16(m, 1H), 7.09–7.01 (m, 1H), 5.53(s, 2H), 4.72(s, 2H)	351
II(c)		5-Bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-ylamine	1.81/ 2.67	(400 MHz, DMSO-d_6) δ 1.75(d, 3H), 6.26(m, 1H), 6.46(s, 2H), 7.28(m, 1H), 7.41(m, 1H), 7.52 (s, 1H)	365
II(d)		5-Bromo-3-[1-(2-chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-pyrazin-2-ylamine	18.1	(400 MHz, DMSO-d_6) δ 0.92(d, 3H), 1.17(m, 3H), 2.57(m, 1H), 5.75(d, 1H), 6.49(s, 2H), 7.24 (m, 1H), 7.40(m, 1H), 7.54(s, 1H)	393
II(e)		5-Bromo-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-ylamine	0.24/ 0.66/1.3	(400 MHz, DMSO-d_6) δ 1.74(d, 3H), 6.40(m, 1H), 6.52(br s, 2H), 7.30(m, 1H), 7.48(m, 1H), 7.56(s, 1H): MS m/z 382 (M + 1).	382
II(f)		5-Bromo-3-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-ylamine			366

TABLE 2

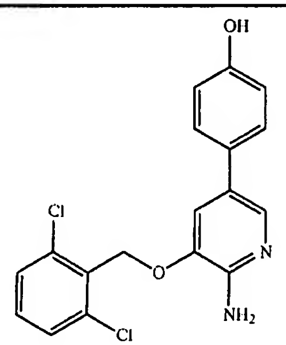
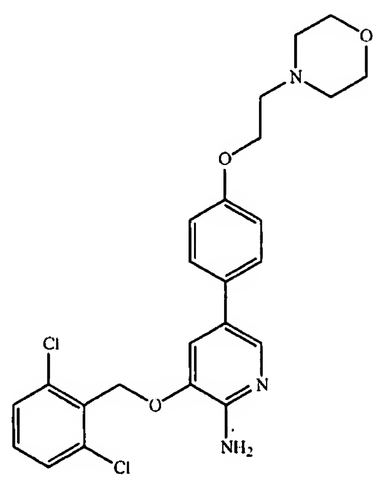
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-1		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol	0.279	see examples	(400 MHz, DMSO-d_6) δ 9.36(s, 1H, OH), 7.77(s, 1H), 7.54(d, J=5.2 Hz, 2H), 7.43 (m, 4H), 6.78(d, J=5.2 Hz, 2H), 5.49(br. s, 2H, NH_2), 5.30(s, 2H, CH_2).	362
I-2		3-(2,6-Dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.58	see examples	(400 MHz, DMSO-d_6) δ 7.81(d, J=1.2 Hz, 1H), 7.53(m, 3H), 7.48(m, 3H), 6.97 (d, 2H), 5.53(br. s 2H, NH_2), 5.31(s, 2H, CH_2). 4.08(t, 2H), 3.55(t, 4H), 2.68(t, 2H), 2.46(t, 4H).	374

TABLE 2-continued

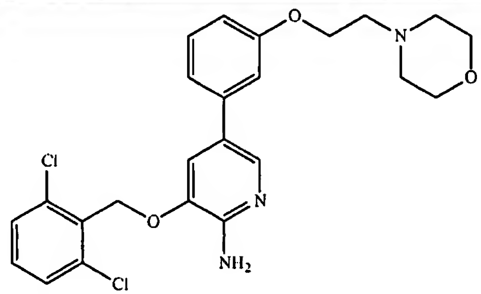
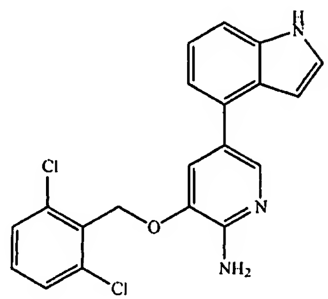
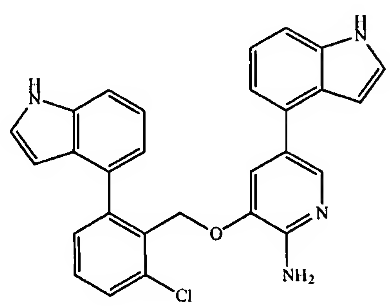
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-3		3-(2,6-Dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.59	see examples	(400 MHz, DMSO-d_6) δ 7.89 (d, J=1.2 Hz, 1H), 7.54(d, J=5.2 Hz, 2H), 7.51(d, J=1.2 Hz, 1H), 7.44(dd, 1H), 7.28(dd, 1H), 7.18(m, 2H), 6.83(dd, 1H), 5.65(br. s, 2H), 5.33(s, 2H), 4.12(t, 2H), 3.55(t, 6H), 2.88(t, 2H), 2.46(t, 2H)	475
I-4		3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine	1.4	see examples	(400 MHz, DMSO-d_6) δ 11.18(s, 1H, NH), 7.87(d, 1H), 7.5(d, 2H), 7.46(d, 2H), 7.36(m, 1H), 7.33(m, 1H), 7.12(t, 1H), 7.03(d, 1H), 6.49(d, 1H), 5.61(br. s, 2H, NH_2), 5.31(s, 2H, CH_2).	384
I-5		3-[2-Chloro-6-(1H-indol-4-yl)-benzyloxy]-5-(1H-indol-4-yl)-pyridin-2-ylamine	4.71	see examples		465

TABLE 2-continued

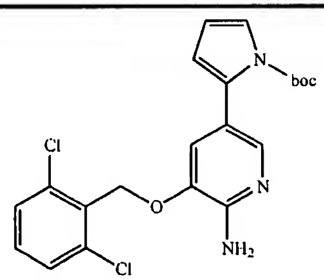
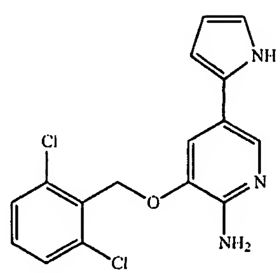
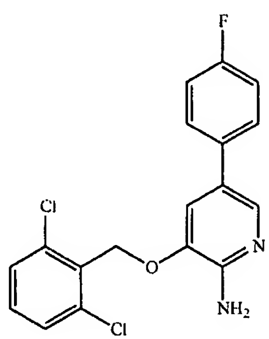
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-6		2-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-pyrrole-1-carboxylic acid tert-butyl ester	>20	see examples		435
I-7		3-(2,6-Dichloro-benzyloxy)-5-(1H-pyrrol-2-yl)-pyridin-2-ylamine	4.25	see examples	(400 MHz, DMSO-d_6) δ 11.05(s, 1H), 7.85(s, 1H), 7.58(s, 1H), 7.55(s, 1H), 7.50(m, 2H), 6.75(s, 1H), 6.35(s, 1H), 6.05(s, 1H), 5.50(br. s, 2H), 5.30(s, 2H).	335
I-8		3-(2,6-Dichloro-benzyloxy)-5-(4-fluoro-phenyl)-pyridin-2-ylamine	8.01	see examples	(400 MHz, DMSO-d_6) δ 7.89(s, 1H), 7.69(m, 2H), 7.58(m, 3H), 7.48(m, 1H), 7.23(m, 2H), 5.70(br. s, 2H), 5.35(s, 2H).	364

TABLE 2-continued

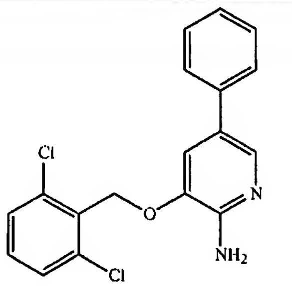
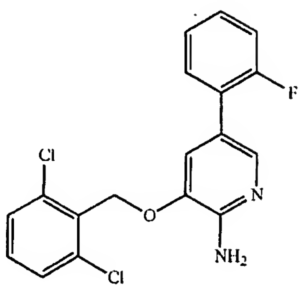
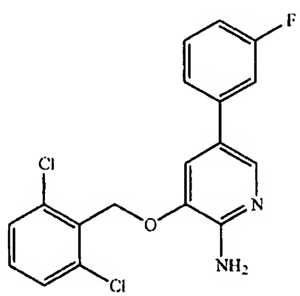
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-9		3-(2,6-Dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine	3.8	see examples	(400 MHz, DMSO-d_6) δ 7.89(d, J=2 Hz, 1H), 7.63(d, J=6.8 Hz, 2H), 7.57(d, J=2 Hz, 1H), 7.54(m, 2H), 7.43(m, 1H), 7.40 (m, 2H), 7.26(m, 1H), 5.68(br. 5, 2H), 5.34(s, 2H).	345
I-10		3-(2,6-Dichloro-benzyloxy)-5-(2-fluoro-phenyl)-pyridin-2-ylamine	6.09	see examples	(400 MHz, DMSO-d_6) δ 7.76(d, 1H), 7.55 (m, 2H), 7.54(m 1H), 7.46(m. 2H), 7.32 (m, 1H), 7.25(m, 2H), 5.78(br. s, 2H), 5.28(s, 2H).	364
I-11		3-(2,6-Dichloro-benzyloxy)-5-(3-fluoro-phenyl)-pyridin-2-ylamine	13.8	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.58–7.44(m, 7H), 7.17(m 1H), 5.78(br. s, 2H), 5.35(s, 2H).	364

TABLE 2-continued

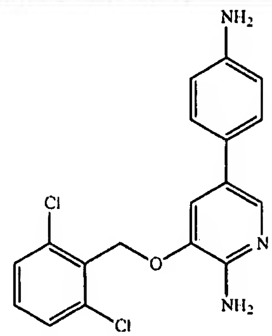
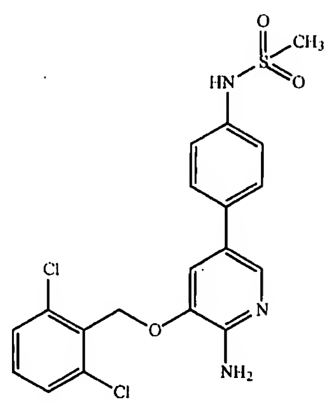
No.	Structure	Name	Met IC_{50} (µM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-12		5-(4-Amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	0.606	see examples	(400 MHz, DMSO-d_6) δ 7.75(d, 1H), 7.54 (dd, 4H), 7.47(m, 1H), 7.40(d, 1H), 7.29 (dd, 2H), 6.60(dd, 2H), 5.44(br. s, 2H), 5.31(s, 2H), 5.15(br s, 2H).	360
I-13		N-{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide	0.44	see examples	(400 MHz, DMSO-d_6) δ 9.70(s, 1H), 7.86(d, 1H), 7.59(m, 1H), 7.56(m, 2H), 7.55(m, 1H), 7.45(m, 2H), 7.22(dd, 2H), 5.63(br. s, 2H), 5.33(s, 2H), 2.95(s, 3H).	439

TABLE 2-continued

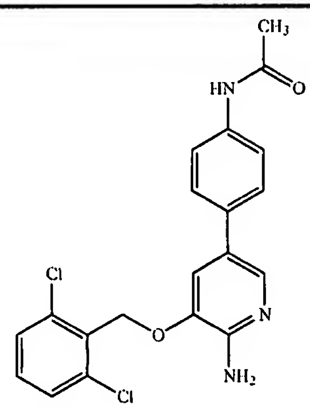
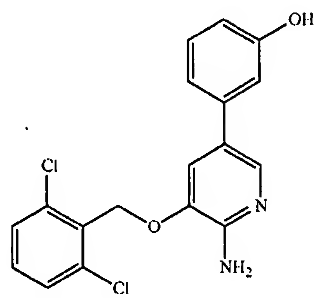
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-14		N-{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-acetamide	>20	see examples	(400 MHz, DMSO-d_6) δ 9.94(s, 1H), 7.86(d, 1H), 7.59(m, 1H), 7.57(m, 2H), 7.54(m, 2H), 7.48(m, 2H), 5.61(br. s, 2H), 5.33(s, 2H), 2.04(s, 3H).	402
I-15		3-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol	1.34	see examples	(400 MHz, DMSO-d_6) δ 7.83(s, 1H), 7.55(dd, 2H), 7.46(m 2H), 7.19(m, 1H), 7.10(m, 1H), 7.04(m, 1H), 6.98(m, 1H), 6.69(m, 1H), 5.67(br. s, 2H), 5.33(s, 2H).	360

TABLE 2-continued

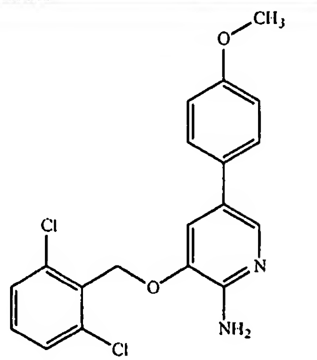
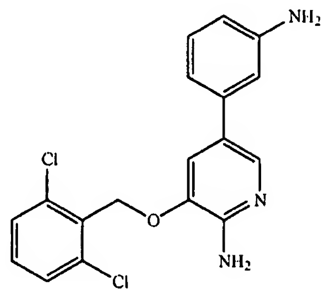
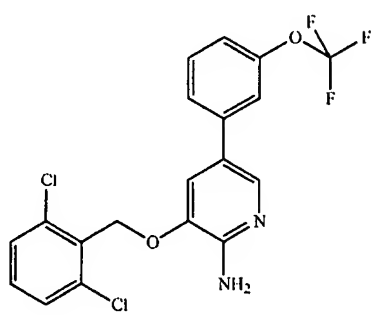
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-16		3-(2,6-Dichloro-benzyloxy)-5-(4-methoxy-phenyl)-pyridin-2-ylamine	6.55	see examples	(400 MHz, DMSO-d_6) δ 7.83(s, 1H), 7.62–7.54(m, 4H), 6.97(dd, 2H), 6.66 (dd, 2H), 5.58(br. s, 2H), 5.33(s, 2H), 3.77(s, 3H).	357
I-17		5-(3-Amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	1.07	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.68 (m, 1H), 7.45(m, 1H), 7.36(t, 1H), 7.28(d, 1H), 7.22(m, 1H), 6.93(d, 1H), 6.86(d, 1H), 6.64(dd, 1H), 5.34(s, 2H), 4.73(br s, 2H), 4.12(br s, 2H).	360
I-18		3-(2,6-Dichloro-benzyloxy)-5-(3-trifluoromethoxy-phenyl)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, 1H), 7.49–7.24(m, 7H), 7.17(m. 1H), 5.39(s, 2H), 4.81(br s, 2H).	429

TABLE 2-continued

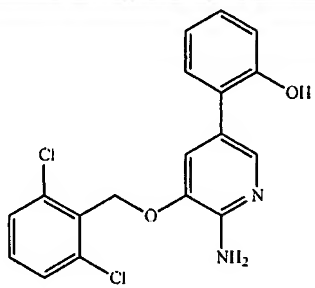
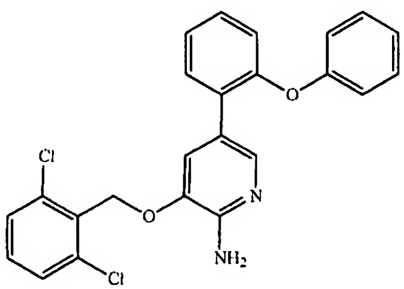
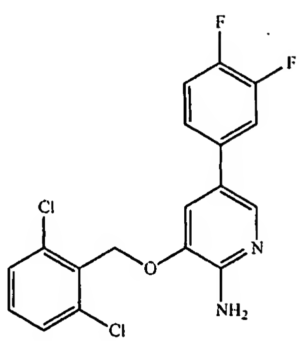
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-19		2-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenol	2.16	see examples	(300 MHz, $CDCl_3$) δ 7.81(d, 1H), 7.66 (m, 2H), 7.52(m, 1H), 7.37(d, 1H), 7.26(m, 3H), 6.99(m, 2H), 5.32(s, 2H), 4.77(br s, 2H)	361
I-20		3-(2,6-Dichloro-benzyloxy)-5-(2-phenoxy-phenyl)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.88(d, 1H), 7.66 (m, 2H), 7.45(m, 3H), 7.34(m, 2H), 7.26(m, 3H), 7.07(m, 2H), 6.93(, 2H), 5.16(s, 2H), 4.66(br s, 2H).	437
I-21		3-(2,6-Dichloro-benzyloxy)-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine	14.3	see examples	(300 MHz, $CDCl_3$) δ 7.89(d, 1H), 7.40 (d, 2H), 7.26(m, 5H), 5.37(s, 2H), 4.80(br s, 2H).	381

TABLE 2-continued

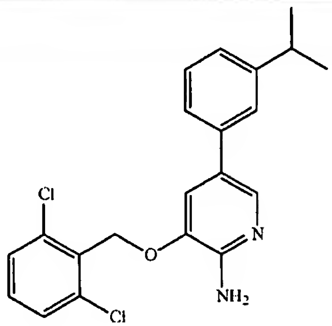
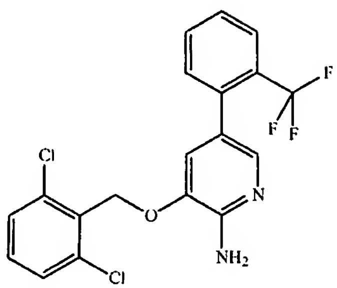
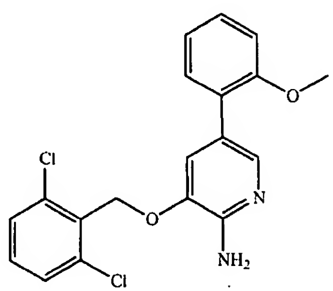
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-22		3-(2,6-Dichloro-benzyloxy)-5-(3-isopropyl-phenyl)-pyridin-2-ylamine	15.9	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, 1H), 7.40–7.15(m, 8H), 5.38(s, 2H), 4.73(br s, 2H), 2.98(m, 1H), 1.31(d, 6H).	387
I-23		3-(2,6-Dichloro-benzyloxy)-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.76(d, J=8.7 Hz, 1H), 7.69(s, 1H), 7.58(t, J=7.3 Hz, 1H), 7.47(t, J=7.4 Hz, 1H), 7.38(d, J=7.4 Hz, 2H), 7.27(m, 2H), 7.17(s, 1H), 5.29(s, 2H), 4.78(br s, 2H).	413
I-24		3-(2,6-Dichloro-benzyloxy)-5-(2-methoxy-phenyl)-pyridin-2-ylamine	11.5	see examples	(300 MHz, $CDCl_3$) δ 7.89(s, 1H), 7.41–7.24(m, 6H), 7.02(m, 2H), 5.32 (s, 2H), 4.69(br s, 2H), 3.84(s, 3H).	375

TABLE 2-continued

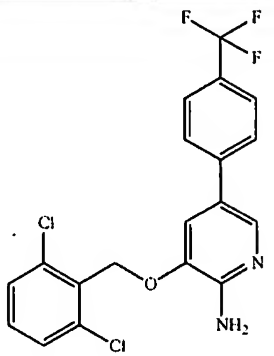
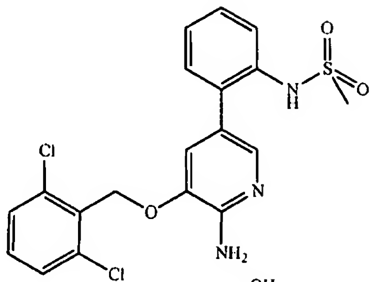
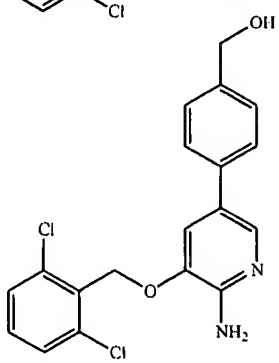
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-25		3-(2,6-Dichloro-benzyloxy)-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.66(m, 3H), 7.36(m, 3H), 7.29(m, 2H), 7.89(s, 1H), 5.38(s, 2H), 4.93(brs, 2H)	413
I-26		N-{2-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide	>20	see examples	(300 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 7.70–7.14(m, 9H), 5.31(s, 2H), 5.16(br s, 2H), 3.16(s, 3H)	438
I-27		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-methanol	2.5	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, J=1.8 Hz, 1H), 7.66(m, 2H), 7.63–7.18(m, 6H), 5.36 (s, 2H), 4.75(d, 2H), 4.73(br s, 2H), 2.5(br, 1H)	375

TABLE 2-continued

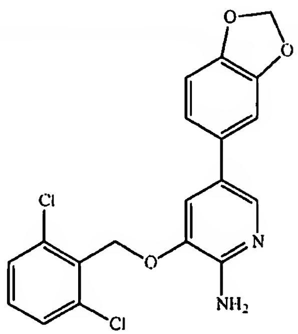
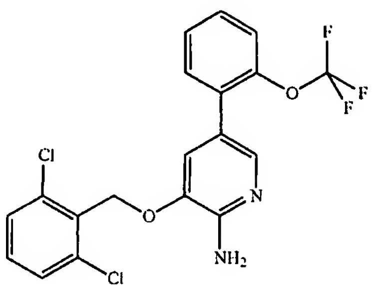
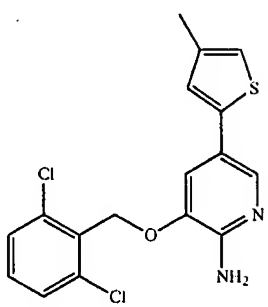
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-28		5-Benzo[1,3]dioxol-5-yl-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	8.5	see examples	(300 MHz, $CDCl_3$) δ 7.88(d, J=1.5 Hz, 1H), 7.37(m, 2H), 7.29(m, 2H), 6.99(d, 2H), 6.87(d, 1H), 5.99(s, 2H), 5.36(s, 2H), 4.74 (br s, 2H)	389
I-29		3-(2,6-Dichloro-benzyloxy)-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.82(s, 1H), 7.47–7.25(m, 8H), 5.33(s, 2H), 4.82(br s, 2H)	429
I-30		3-(2,6-Dichloro-benzyloxy)-5-(4-methyl-thiophen-2-yl)-pyridin-2-ylamine	3.5	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.9 Hz, 1H), 7.37 d, J=8.5 Hz, 2H), 7.29(m, 2H), 7.00(d, J=1.1 Hz, 1H), 6.80(s, 1H), 5.34(s, 2H), 4.80(br s, 2H), 2.28(s, 3H)	365

TABLE 2-continued

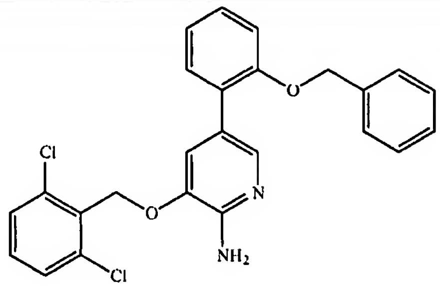
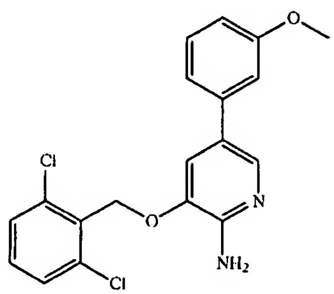
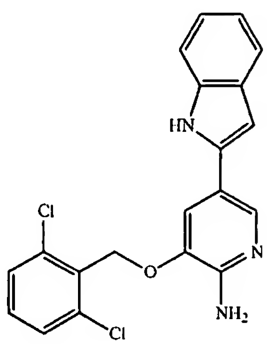
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-31		5-(2-Benzyloxy-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 7.90(d, J=1.7 Hz, 1H), 7.49(d, J=1.7 Hz, 1H), 7.31(m, 10H), 7.06(m, 2H), 5.06(s, 2H), 4.77(br s, 2H).	451
I-32		3-(2,6-Dichloro-benzyloxy)-5-(3-methoxy-phenyl)-pyridin-2-ylamine	4.01	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.39–7.11(m, 4H), 7.13(d, J=7.7 Hz, 2H), 7.07(t, J=2.1 Hz, 1H), 6.88(dd, J=8.2 Hz, 2.1 Hz, 1H), 5.36(s, 2H), 4.78(br s, 2H), 3.87(s, 3H).	375
I-33		3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-2-yl)-pyridin-2-ylamine	7.5	see examples	(300 MHz, $CDCl_3$) δ 8.47(br s, 1H), 8.04(s, 1H), 7.70(d, J=5.5 Hz, 1H), 7.62–7.11(m, 6H), 6.71(d, J=1.3 Hz, 1H), 6.66(dd, J=7.7 Hz, 2.1 Hz, 1H), 5.29(s, 2H), 4.73(br s, 2H).	384

TABLE 2-continued

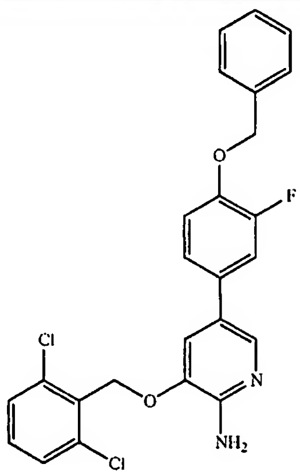
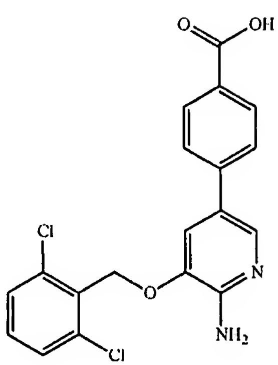
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-34		5-(4-Benzyloxy-3-fluoro-phenyl)-3-(2,6-dichloro-benzyloxy)-pyridin-2-ylamine	13.5	see examples	(400 MHz, DMSO-d_6) δ 5.20(s, 2H), 5.32(s, 2H), 5.65(s, 2H), 7.25(t, 1H), 7.33(m, 1H), 7.39(m, 3H), 7.46(m, 3H), 7.51(m, 4H), 7.88(s, 1H)	469
I-35		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid	12.8	see examples	(400 MHz, DMSO-d_6) δ 7.98(s, 1H), 7.92(d, J=5.6 Hz, 2H), 7.75(d, J=4.8 Hz, 2H), 7.55(d, J=5.2 Hz, 1H), 7.54(dd, 2H), 7.45(m, 1H), 5.8(br. s, 2H), 5.34(s, 2H).	390

TABLE 2-continued

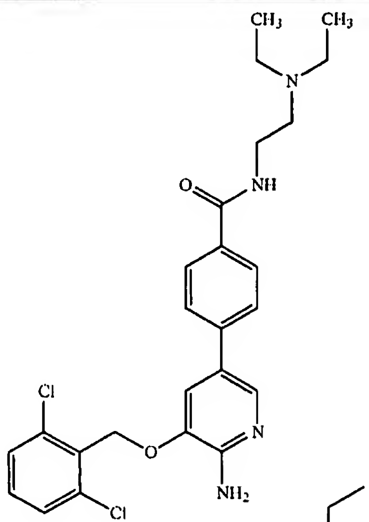
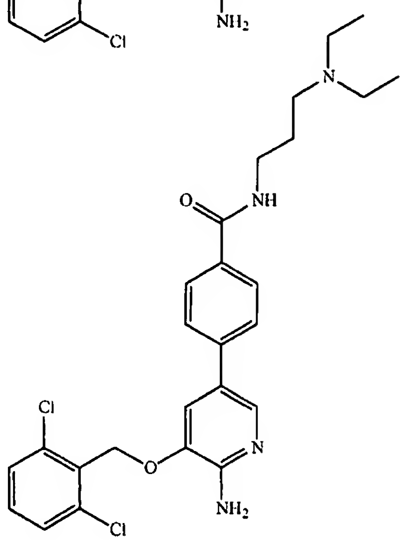
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-36		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-diethylamino-ethyl)-benzamide	0.99	see examples	(400 MHz, DMSO-d_6) δ 8.45(s, 1H), 7.97(d, J=1.2 Hz, 1H), 7.86(d, J=5.6 Hz, 2H), 7.73(d, J=5.6 Hz, 2H), 7.60(d, J=1.2 Hz, 1H), 7.54(d, J=5.2 Hz, 2H), 7.44(dd, 1H), 5.77(br. s, 2H), 5.34(s, 2H), 3.3(m, 4H), 2.6(m, 4H), 0.99(t, 6H)	487
I-37		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-diethylamino-propyl)-benzamide	0.82	see examples	(400 MHz, DMSO-d_6) δ 8.60(s, 1H), 7.95(d, J=1.2 Hz, 1H), 7.85(d, J=5.6 Hz, 1H), 7.75(d, J=5.6 Hz, 1H), 7.70(d, J=1.2 Hz, 1H), 7.60(m, 1H), 7.55 (m, 2H), 7.45(m, 2H), 5.70(br. s, 2H), 5.35 (s, 2H), 3.3(m, 4H), 2.6(m, 4H), 1.7(m, 2H), 1.0(t, 6H)	501

TABLE 2-continued

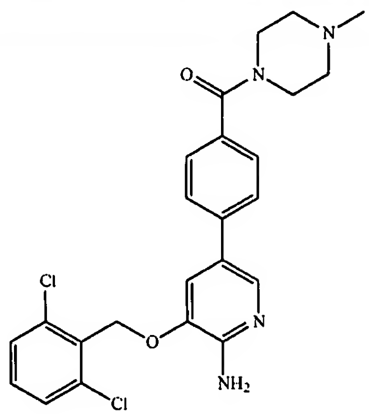
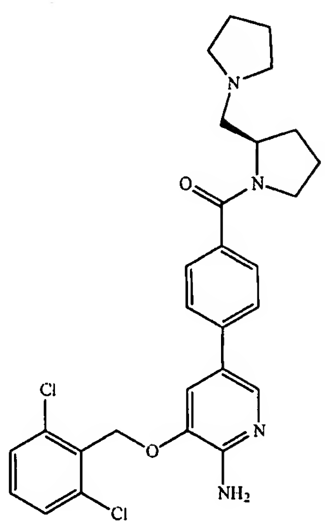
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-38		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	1.02	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, J=2 Hz, 1H), 7.72(dd, J=6, 1.6 Hz, 2H), 7.59(d, J=1.6 Hz, 1H), 7.57(d, J=1.2 Hz, 1H), 7.55(s, 1H), 7.43(dd, J=6, 1.2 Hz, 1H), 7.40(dd, J=6, 1.6 Hz, 2H), 5.76(br. s, 2H), 5.35(s, 2H), 3.6(m, 4H), 2.3(m, 4H), 2.2(s, 3H).	471
I-39	 Chiral	{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.062/ 0.11/0.2 (Ki 0.04)	see examples	(400 MHz, DMSO-d_6) δ 7.96(d, 1H), 7.72(dd, 2H), 7.59(m, 2H), 7.54(m, 2H), 7.47(m, 2H), 5.76(br. s, 2H), 5.36(s, 2H), 4.35(m, 1H), 3.5(d, 2H), 3.0(m, 4H), 1.7–2.0(m, 10H).	525

TABLE 2-continued

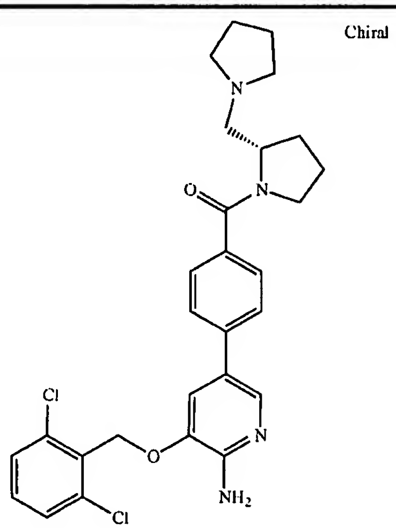
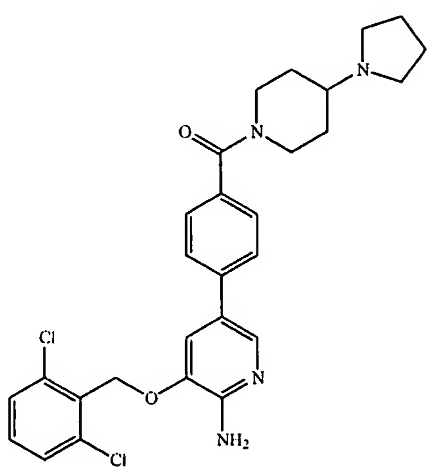
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-40		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.21	see examples	(400 MHz, DMSO-d_6) δ 7.93(d, 1H), 7.68(dd, 2H), 7.57(d, 1H), 7.54(dd, 2H), 7.47(m, 2H), 7.44(m, 1H), 5.74(br. s, 2H), 5.34(s, 2H), 3.45(m, 1H), 3.3(m, 4H), 2.46(m, 2H), 1.95(m, 2H), 1.84(m, 4H), 1.63(m, 4H).	526
I-41		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.35	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.70(dd, 2H), 7.55(d, 1H), 7.48(dd, 2H), 7.41(m, 1H), 7.39(m, 2H), 5.76(br. s, 2H), 5.35(s, 2H), 3.0(m, 4H), 2.6(m, 4H), 2.25(s, 1H), 1.89(m, 4H), 1.66(m, 4H)	525

TABLE 2-continued

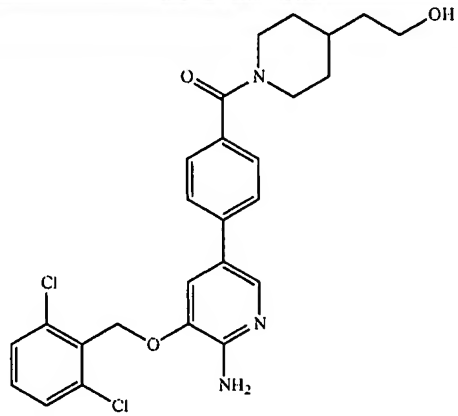
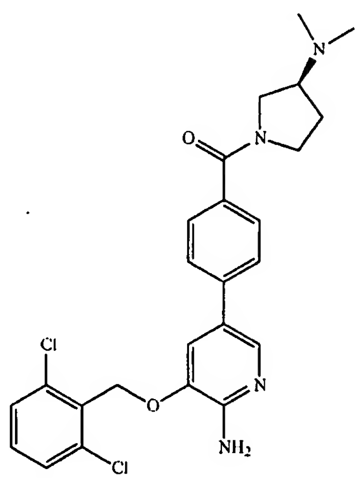
No.	Structure	Name	Met IC_{50} (µM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-42		{4-(6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone	0.56	see examples	(400 MHz, DMSO-d_6) δ 7.94(d, 1H), 7.71(dd, 2H), 7.70(d, 1H), 7.59(dd, 2H), 7.55(m, 1H), 7.45(m, 2H), 5.76(br. s, 2H), 5.35(s. 2H), 4.35(t, 2H), 3.60(m, 1H), 3.44(m, 2H), 3.0(m, 2H), 1.68(m, 2H), 1.40(m, 2H), 1.37(m, 2H)	500
I-43		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.47	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.75(dd, 2H), 7.57(d, 1H), 7.55(dd, 2H), 7.48(m, 1H), 7.46(m, 2H), 5.76(br. s, 2H), 5.35(s, 2H), 3.60(m, 1H), 3.0(m, 2H), 2.2 (s, 3H), 2.1(s, 3H), 1.15(m, 2H)	485

TABLE 2-continued

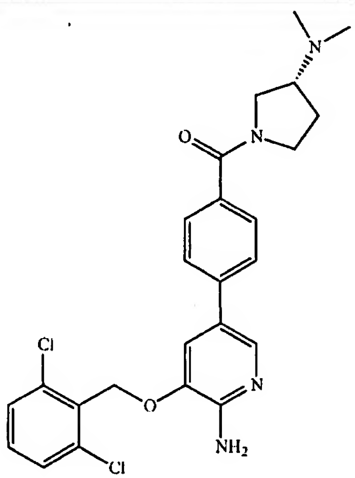
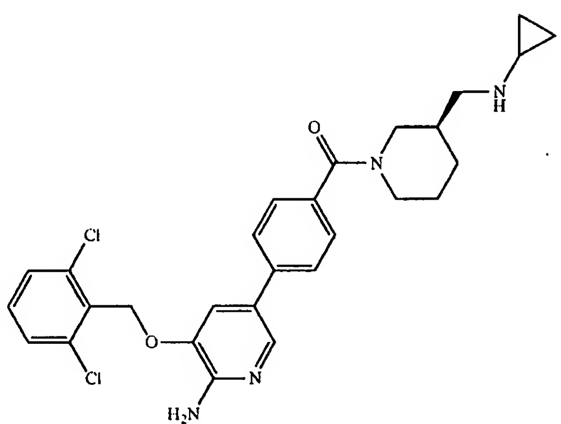
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-44		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.65	see examples	(400 MHz, DMSO-d_6) δ 7.95(m, 1H), 7.72(m, 2H), 7.60(m, 1H), 7.55(m, 2H), 7.46(m, 3H), 5.76(br. s, 2H), 5.35(s, 2H), 3.50(m, 3H), 3.0(m, 2H), 2.1(s, 3H), 2.05 (s, 3H), 1.1(m, 2H)	485
I-45		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-cyclopropylaminomethyl-piperidin-1-yl]-methanone	0.77	see examples	(400 MHz, DMSO-d_6) δ 7.94(d, 1H), 7.77(m, 2H), 7.57(m, 2H), 7.55(m, 1H), 7.46(dd, 1H), 7.39(m, 2H), 5.79(s, 2H), 5.35(s, 2H), 4.4(m, 1H), 3.6(m, 1H), 2.6–3.0(m, 4H), 1.4–1.8(m, 8H), 0.8(m, 2H).	526

TABLE 2-continued

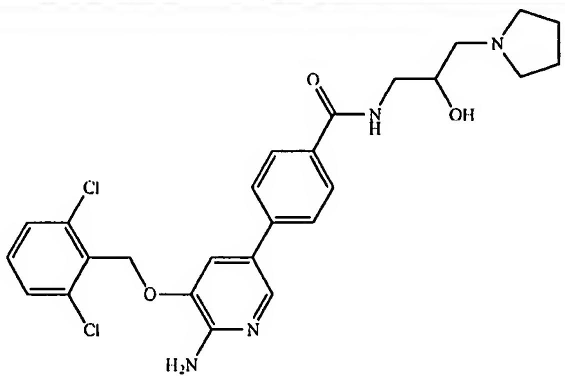
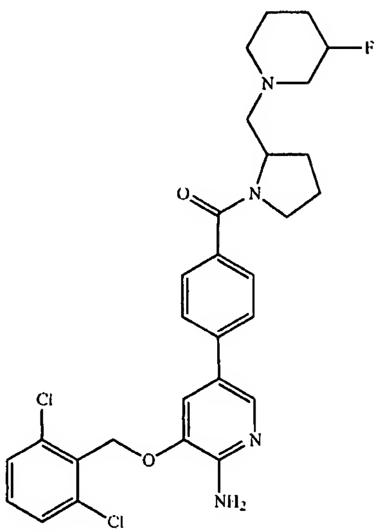
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-46		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide	0.2	see examples	(400 MHz, DMSO-d_6) δ 8.48(m, 1H), 7.99(d, 2H), 7.88(m, 2H), 7.75(m, 2H), 7.61(d, 1H), 7.57(m, 2H), 7.46(dd, 1H), 5.79(s, 2H), 5.36(s, 2H), 4.8(m, 1H), 3.75(m, 1H), 3.44(m, 1H), 3.18(m, 1H), 2.53(m, 4H), 2.40(m, 1H), 1.67(m, 4H)	515
I-47		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-(3-fluoro-piperidin-1-ylmethyl)-pyrrolidin-1-yl]-methanone	0.42	see examples		557

TABLE 2-continued

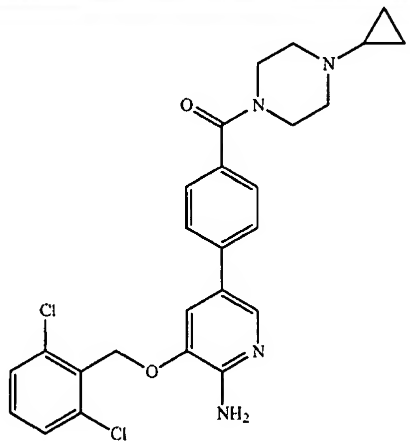
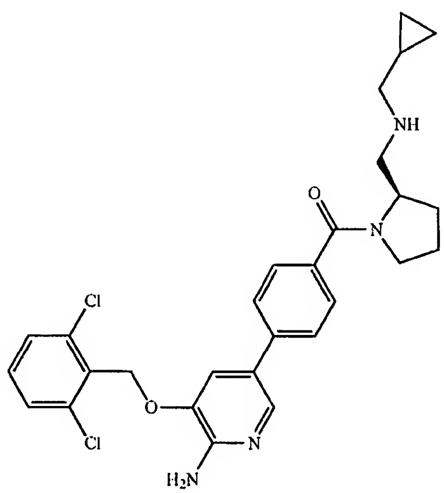
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-48		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-cyclopropyl-piperazin-1-yl)-methanone	1.67	see examples		497
I-49		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-{(2R)-2-[(cyclopropylmethyl-amino)-methyl]-pyrrolidin-1-yl}-methanone	0.37	see examples	(400 MHz, DMSO-d_6) δ 7.92(d, 1H), 7.67 (m, 2H), 7.54(m, 2H), 7.49(m, 2H), 7.43 (m, 2H), 5.73(s, 2H), 5.32(s, 2H), 4.2(m, 1H), 3.5(m, 1H), 3.28(m, 4H), 2.0–1.7(m, 6H), 1.18(m, 4H)	525

TABLE 2-continued

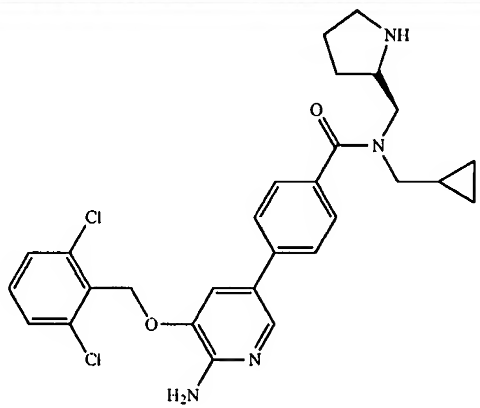
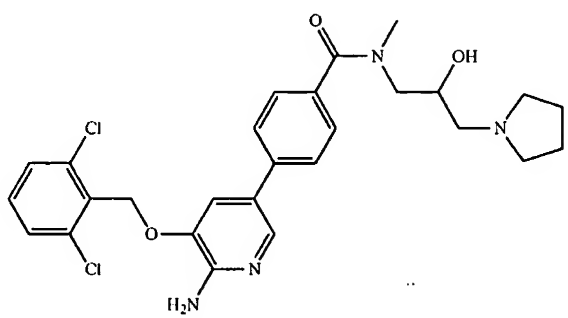
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-50		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-cyclopropylmethyl-N-(2R)-pyrrolidin-2-ylmethyl-benzamide	0.29	see examples	(400 MHz, DMSO-d_6) δ 8.16(d, 1H), 7.61 (d, 1H), 7.38(m, 2H), 7.23-7.18(m, 4H), 7.09(m, 1H), 5.44(s, 2H), 4.98(s, 2H), 4.05(m, 1H), 3.2(m, 1H), 3.1(m, 1H), 2.93(m, 8H), 2.78(m, 2H), 2.10(m, 4H)	525
I-51		4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-hydroxy-3-pyrrolidin-1-yl-propyl)-N-methyl-benzamide	0.71	see examples	(400 MHz, DMSO-d_6) δ 7.90(m, 1H), 7.76 (m, 1H), 7.63(m, 2H), 7.52(d, 2H), 7.50 (m, 2H), 7.40(m, 1H), 5.69(s, 2H), 5.30(s, 2H), 3.70(m, 1H), 2.96(s, 3H), 2.44(m, 4H), 2.34(m, 4H), 1.75(m, 4H).	529

TABLE 2-continued

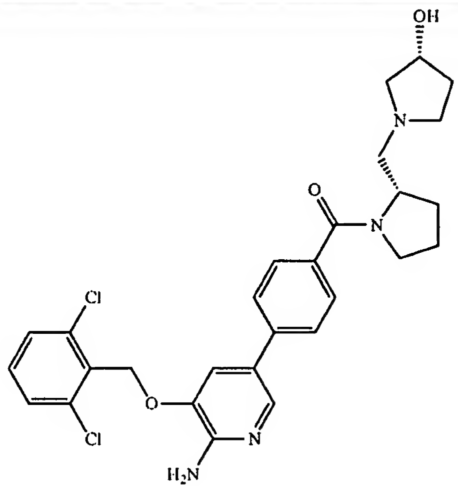
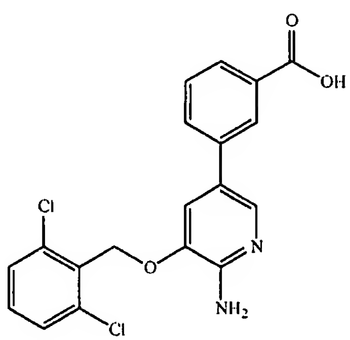
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-52		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-{(2S)-2-[(3R)-3-hydroxy-pyrrolidin-1-ylmethyl]-pyrrolidin-1-yl}-methanone	0.53	see examples	(400 MHz, DMSO-d_6) δ 7.96(d, 1H), 7.70 (m, 2H), 7.60(m, 1H), 7.57(m, 1H), 7.55(m, 3H), 7.46(m, 1H), 5.78(s, 2H), 5.37(s, 2H), 4.3(m, 1H), 3.6(m, 4H), 3.2(m, 4H), 1.9(m, 4H), 1.24(m, 4H).	541
I-53		3-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid	16	see examples	(400 MHz, DMSO-d_6) δ 8.13(m, 1H), 7.91 (d, 1H), 7.98(m, 2H), 7.56(dd, 2H), 7.54(m, 2H), 7.47(m, 1H), 5.76(s, 2H), 5.36(s, 2H)	389

TABLE 2-continued

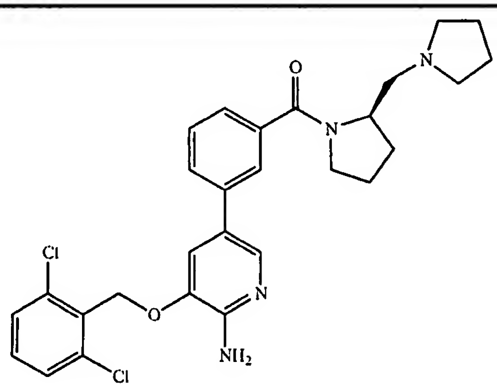
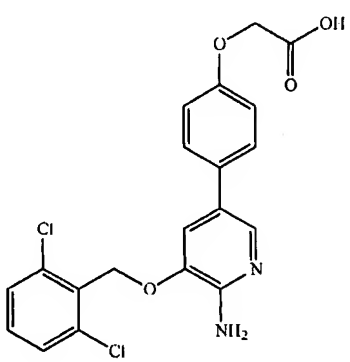
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-54		{3-(6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	2.5	see examples	(400 MHz, DMSO-d_6) δ 7.93(d, 1H), 7.74 (m, 2H), 7.56(m, 3H), 7.46(m, 2H), 7.36(m, 1H), 5.74(s, 2H), 5.35(s, 2H), 4.40(m, 1H), 3.40(d, 2H), 3.0(m, 4H), 1.7–2.0(m, 10H)	525
I-55		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid	2.41	see examples	(400 MHz, DMSO-d_6) δ 7.81(d, 1H), 7.56 (m, 2H), 7.48(m, 4H), 6.87(m, 2H), 5.53(s, 2H), 5.32(s, 2H), 4.33(s, 2H)	419

TABLE 2-continued

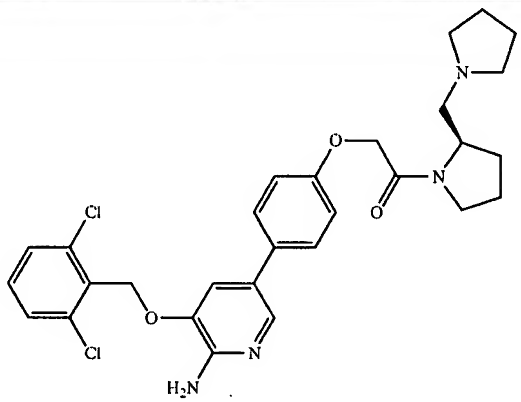
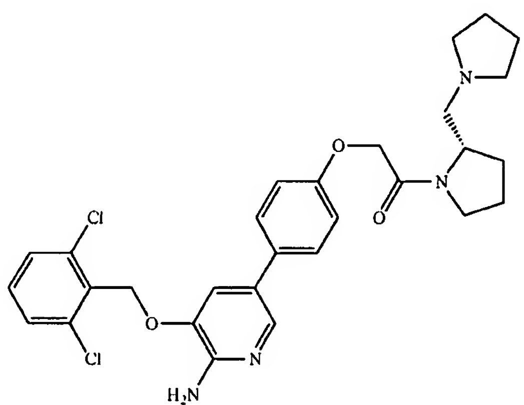
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-56		2-{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone	0.53	see examples	(400 MHz, DMSO-d_6) δ 7.77(d, 1H), 7.52(d, 1H), 7.47(m, 3H), 7.41(m, 2H), 6.88(m, 2H), 5.51(s, 2H), 5.28(s, 2H), 4.67(s, 2H), 4.20(m, 1H), 3.42(m, 2H), 1.82(m, 4H), 1.96(m, 10H).	555
I-57		2-{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone	0.5	see examples	(400 MHz, DMSO-d_6) δ 7.82(d, 1H), 7.57(d, 1H), 7.52(m, 3H), 7.45(m, 2H), 6.93(m, 2H), 5.56(s, 2H), 5.33(s, 2H), 4.72(s, 2H), 4.20(m, 1H), 3.5(m, 2H), 2.52(m, 6H), 1.85(m, 4H), 1.66(m, 4H)	555

TABLE 2-continued

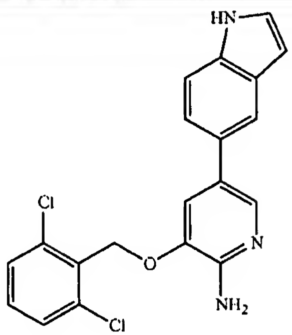
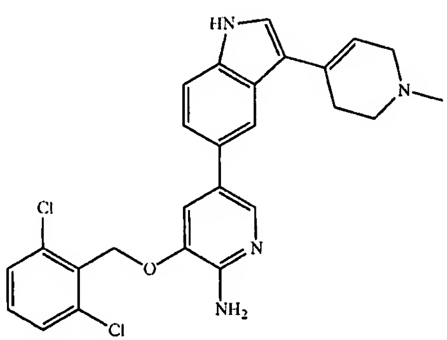
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-58		3-(2,6-Dichloro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine	4.3	see examples	(400 MHz, DMSO-d_6) δ 11.05(s, 1H, NH), 7.87(d, 1H), 7.76(m, 1H), 7.57(m, 3H), 7.40–7.48(m, 2H), 7.34(m, 2H), 6.44(m, 1H), 5.49(br. s, 2H, NH_2), 5.36(s, 2H, CH_2)	384
I-59		3-(2,6-Dichloro-benzyloxy)-5-[3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine	1.57	see examples	(400 MHz, DMSO-d_6) δ 11.35(d, 1H, NH), 7.95(s, 1H), 7.89(d, 1H), 7.55(m, 4H), 7.45(m, 2H), 7.39(dd, 1H), 6.25(m, 1H), 5.54(br. s, 2H, NH_2), 5.37(s, 2H, CH_2), 3.77(m, 2H), 3.32(m, 2H), 2.82(m, 2H), 2.80(s, 3H).	480

TABLE 2-continued

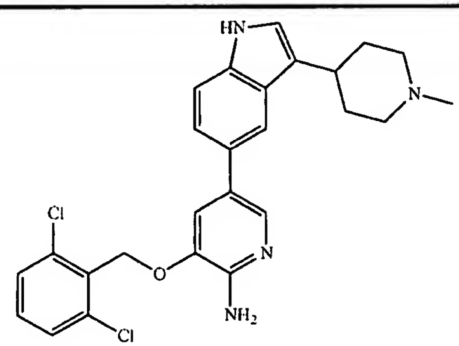
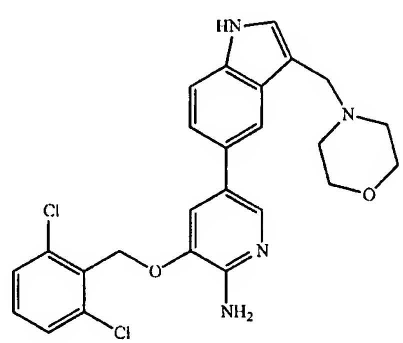
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-60		3-(2,6-Dichloro-benzyloxy)-5-[3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-pyridin-2-ylamine	3.04	see examples	(400 MHz, DMSO-d_6) δ 10.9(d, 1H, NH), 7.90(d, 1H), 7.80(s, 1H), 7.55(m, 4H), 7.46(m, 2H), 7.32(dd, 1H), 5.50(br. s, 2H, NH_2), 5.38(s, 2H, CH_2), 3.32(m, 2H), 3.02(m, 2H), 2.90(m, 1H), 2.67(s, 3H), 2.10(m, 2H), 1.98(m, 2H).	481
I-61		3-(2,6-Dichloro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	1.19	see examples	(400 MHz, DMSO-d_6) δ 2.31(m, 4H), 3.55(m, 4H), 3.66(s, 2H), 5.26(s, 2H), 5.45(s, 2H), 7.22(s, 1H), 7.34(m, 2H), 7.48(m, 2H), 7.57(m, 2H), 7.80(s, 1H), 7.85(s, 1H), 10.92(br s, 1H)	483

TABLE 2-continued

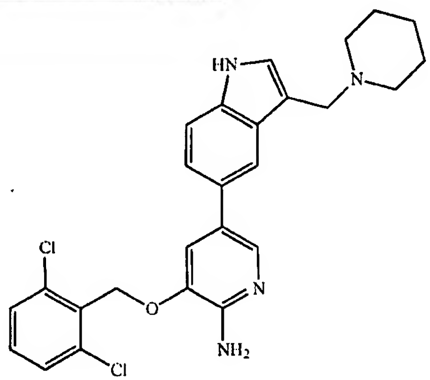
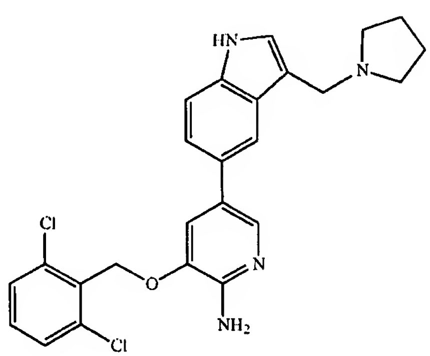
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-62		3-(2,6-Dichloro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	1.41	see examples	(300 MHz, $CDCl_3$) δ 1.43(m, 2H), 1.60(m, 4H), 2.50(m, 4H), 3.76(s, 2H), 4.65(br s, 2H), 5.40(s, 2H), 7.19(s, 1H), 7.27(m, 1H), 7.38(m, 5H), 7.87(s, 1H), 8.01(d, J=1.7 Hz, 1H), 8.17(br s, 1H)	481
I-63		3-(2,6-Dichloro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	1.34	see examples	(300 MHz, $CDCl_3$) δ 1.79(m, 4H), 2.62(m, 4H), 3.88(s, 2H), 4.64(br s, 2H), 5.40(s, 2H), 7.21(d, J=2.3 Hz, 1H), 7.26(m, 1H), 7.38(m, 5H), 7.84(s, 1H), 8.01(d, J=1.8 Hz, 1H), 8.10(br s, 1H)	467

TABLE 2-continued

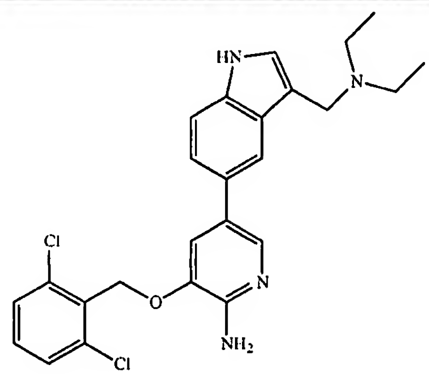
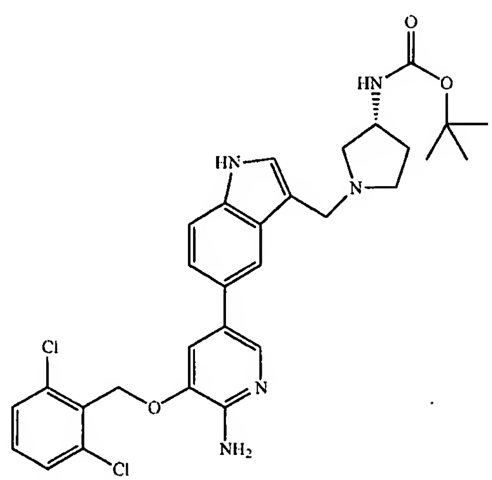
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-64		3-(2,6-Dichloro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-yl)-pyridin-2-ylamine	3.23	see examples	(300 MHz, $CDCl_3$) δ 1.13(t, 6H), 2.64(q, 4H), 3.88(s, 2H), 4.66(br s, 2H), 5.37(s, 2H), 7.19(d, J=1.7 Hz, 1H), 7.26(m, 1H), 7.37(m, 5H), 7.86(s, 1H), 8.00(d, J=1.7 Hz, 1H), 8.44(br s, 1H)	469
I-65		(1-{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-carbamic acid tert-butyl ester	6.3	see examples	(300 MHz, $CDCl_3$) δ 1.39(s, 9H), 2.22(m, 1H), 2.40(m, 1H), 2.58(m, 1H), 2.68(m, 1H), 2.99(m, 1H), 3.82(d, 1H), 3.88(d, 1H), 4.16(m, 1H), 4.65(brs, 2H), 4.81(m, 1H), 5.41(s, 2H), 7.17(d, J=2.1 Hz, 1H), 7.26(m, 1H), 7.38(m, 5H), 7.81(s, 1H), 8.00(d, J=1.8 Hz, 1H), 8.09(br s, 1H)	582

TABLE 2-continued

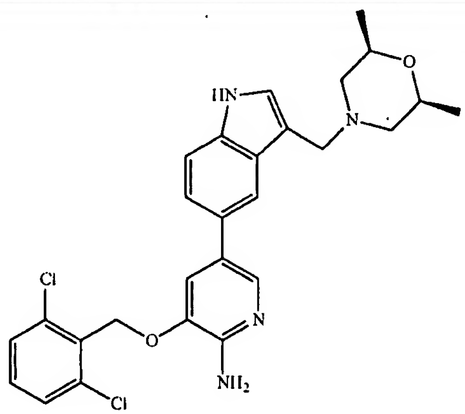
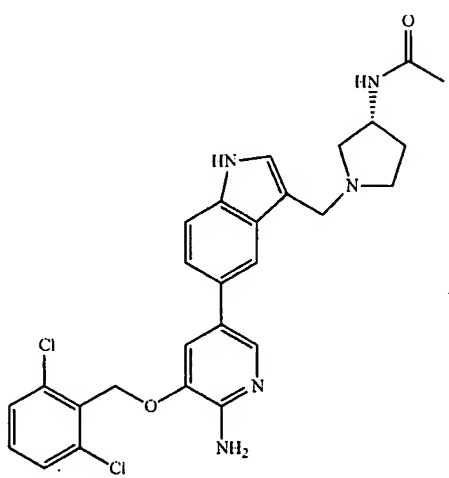
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-66		3-(2,6-Dichloro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyridin-2-ylamine	>20	see examples	(300 MHz, $CDCl_3$) δ 1.13(d, J=6.3 Hz, 6H), 1.80(t, J=10.7 Hz, 2H), 1.94(br s, 1H), 2.84 (d, J=10.5 Hz, 2H), 3.72(m, 4H), 4.68(br s, 2H), 5.39(s, 2H), 7.16(d, J=2.2 Hz, 1H), 7.26(m, 1H), 7.38(m, 5H), 7.89(s, 1H), 8.10(d, J=1.7 Hz, 1H), 8.32(br s, 1H)	511
I-67		N-(1-{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3R)-pyrrolidin-3-yl)-acetamide	1.79	see examples	(300 MHz, $CDCl_3$) δ 1.86(s, 3H), 2.31(m, 2H), 2.59(m, 1H), 2.70(m, 1H), 2.99(m, 1H), 3.82(d, 1H), 3.90(d, 1H), 4.42(m, 1H), 4.68(br s, 2H), 5.40(s, 2H), 5.91(m, 1H), 7.15(d, J=2.2 Hz, 1H), 7.26(m, 2H), 7.38(m, 5H), 7.82(s, 1H), 8.00(d, J=1.8 Hz, 1H), 8.33(br s, 1H)	524

TABLE 2-continued

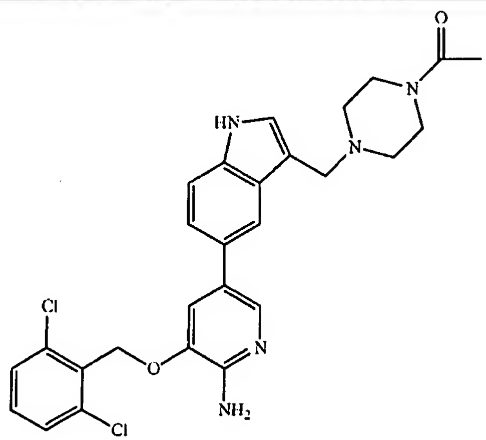
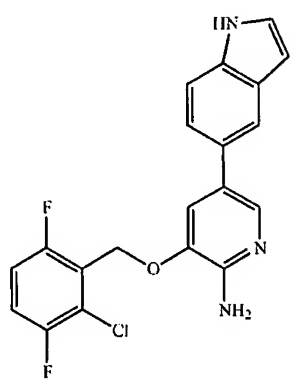
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-68		1-(4-{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone	2.18	see examples	(300 MHz, $CDCl_3$) δ 2.07(s, 3H), 2.51(m, 4H), 3.44(m, 2H), 3.63(m, 2H), 3.78(s, 2H), 4.68(br s, 2H), 5.40(s, 2H), 7.17(d, J=2.2 Hz, 1H), 7.26(m, 1H), 7.38(m, 5H), 7.88(s, 1H), 8.00(d, J=1.8 Hz, 1H), 8.34(br s, 1H)	524
I-69		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyridin-2-ylamine		see examples		386

TABLE 2-continued

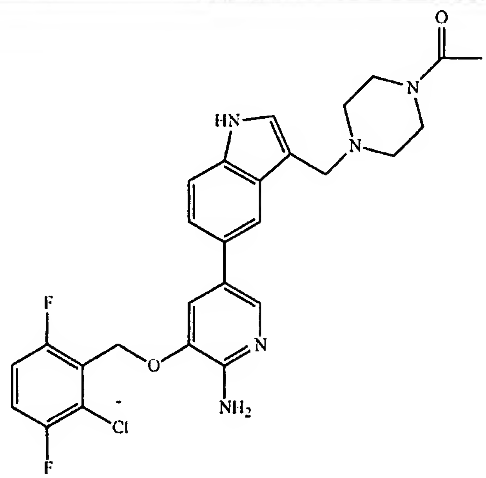
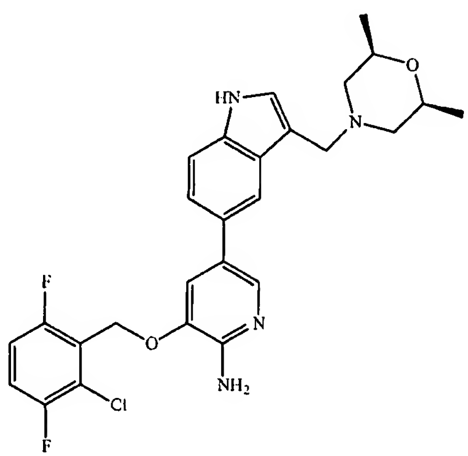
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-70		1-(4-{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone	0.8	see examples	(300 MHz, $CDCl_3$) δ 2.08(s, 3H), 2.49(m, 4H), 3.48(m, 2H), 3.61(m, 2H), 3.80(s, 2H), 4.68(s, 2H), 5.30(s, 2H), 7.02(m, 1H), 7.20(m, 2H), 7.41(m, 3H), 7.89(s, 1H), 8.06(s, 1H), 8.63(s, 1H)	526
I-71		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyridin-2-ylamine	2.71	see examples	(300 MHz, $CDCl_3$) δ 1.37(d, 6H), 1.92(m, 2H), 2.95(m, 2H), 3.87(m, 4H), 4.68(s, 2H), 5.34(s, 2H), 7.08(m, 1H), 7.27(m, 2H), 7.48(m, 3H), 7.89(s, 1H), 7.98(s, 1H), 8.21(br s, 1H)	513

TABLE 2-continued

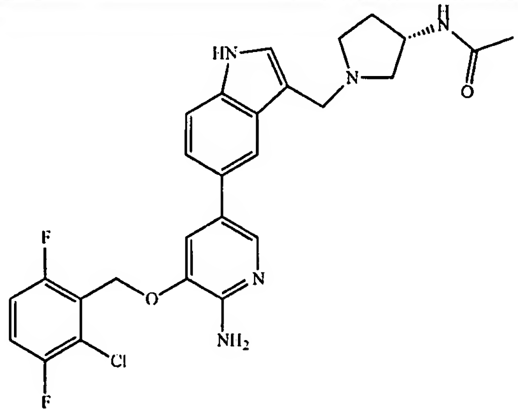
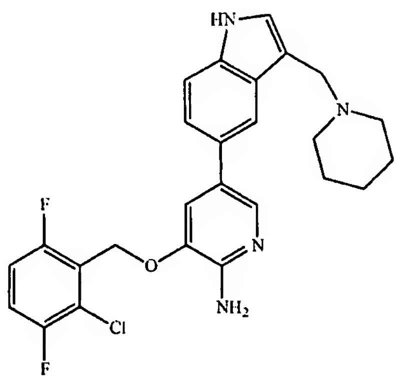
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-72		N-(1-{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide	0.95	see examples	(300 MHz, $CDCl_3$) δ 1.71(m, 1H), 1.81(s, 3H), 2.31(m, 2H), 2.48(m, 1H), 2.79(m, 2H), 3.11(m, 1H), 3.98(m, 2H), 4.68(s, 2H), 5.31(s, 2H), 7.06(m, 1H), 7.20(m, 2H), 7.45(m, 4H), 7.86(s, 1H), 7.98(s, 1H), 8.38(s, 1H)	526
I-73		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	0.74	see examples	.(300 MHz, $CDCl_3$) δ 1.84(m, 2H), 1.64(m, 4H), 2.56(m, 4H), 3.80(s, 2H), 4.68(s. 2H), 5.30(s, 2H), 7.08(m, 1H), 7.20(m, 2H), 7.45(m, 3H), 7.86(s, 1H), 7.89(s, 1H), 8.49(br s, 1H)	483

TABLE 2-continued

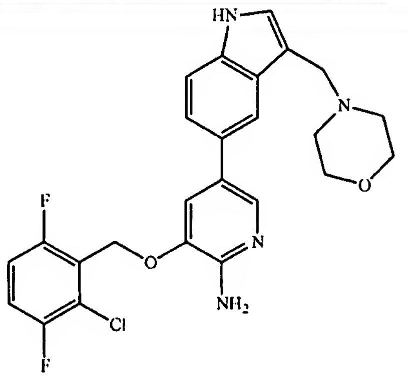
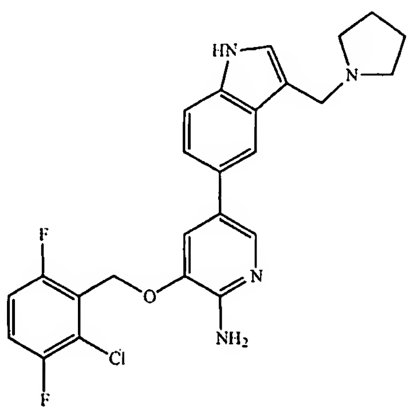
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-74		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	1.4	see examples	(300 MHz, $CDCl_3$) δ 2.72(m, 4H), 3.80(m, 6H), 4.70(s, 2H), 5.33(d, 2H), 7.07(m, 1H), 7.20(m, 1H), 7.35–7.55(m, 4H), 7.86 (s, 1H), 8.00(d, 1H), 8.23(s, 1H)	485
I-75		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyridin-2-ylamine	0.7	see examples	(300 MHz, $CDCl_3$) δ 1.86(m, 4H), 2.79(m, 4H), 4.01(s, 2H), 4.63(s, 2H), 5.30(d, 2H), 7.05(m, 1H), 7.18(m, 1H), 7.30-7.60 (m, 4H), 7.80(s, 1H), 8.00(d, 1H), 8.64(s, 1H)	469

TABLE 2-continued

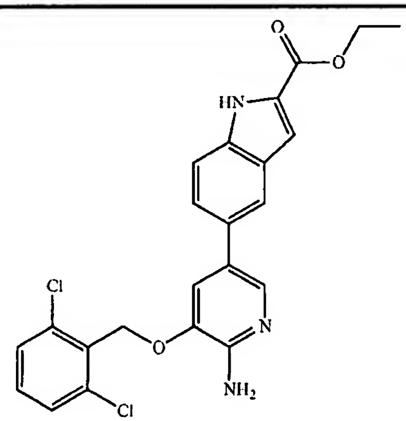
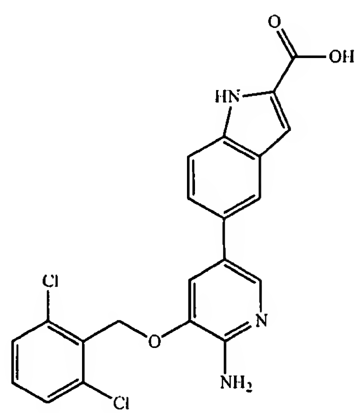
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-76		5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid ethyl ester	>20	see examples	(400 MHz, DMSO-d_6) δ 1.34(t, 3H), 4.34 (m, 2H), 5.34(s, 2H), 5.58(s, 2H), 7.16(s, 1H), 7.52(m, 6H), 7.84(d, 2H), 11.84(s, 1H)	456
I-77		5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid	1.62	see examples	(400 MHz, DMSO-d_6) δ 5.46(s, 2H), 5.53 (s, 2H), 6.66(s, 1H), 7.33(d, 1H), 7.44(m, 2H), 7.54(m, 3H), 7.72(s, 1H), 7.86(s, 1H), 11.12(s, 1H)	428

TABLE 2-continued

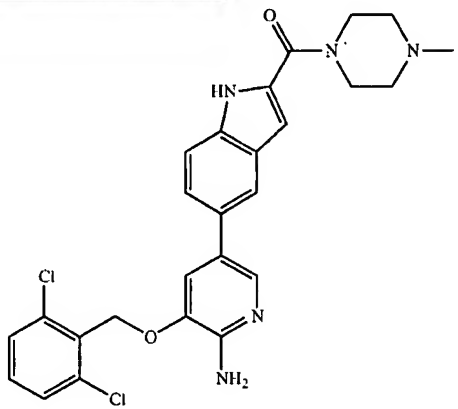
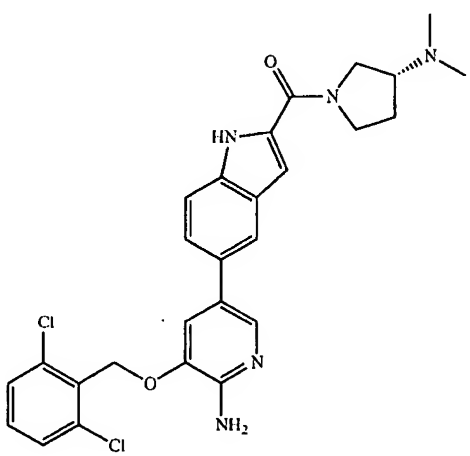
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-78		{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-(4-methyl-piperazin-2-yl)-methanone	0.18	see examples	(400 MHz, DMSO-d_6) δ 2.21(s, 3H), 2.36 (m, 4H), 3.74(m, 4H), 5.35(s, 2H), 5.53(s, 2H), 6.78(s, 1H), 7.50(m, 6H), 7.81(s, 1H), 7.88(s, 1H), 11.56(s, 1H)	510
I-79		{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.18	see examples	(400 MHz, DMSO-d_6) δ 1.80(m, 1H), 2.12 (m, 1H), 2.21(s, 6H), 2.74(m, 1H), 3.25(m, 1H), 3.53(m, 1H), 3.78(m, 1H), 4.02(m, 1H), 5.36(s, 2H), 5.54(s, 2H), 6.98(s, 1H), 7.46(m, 3H), 7.56(m, 3H), 7.86(m, 2H), 11.56(s, 1H)	524

TABLE 2-continued

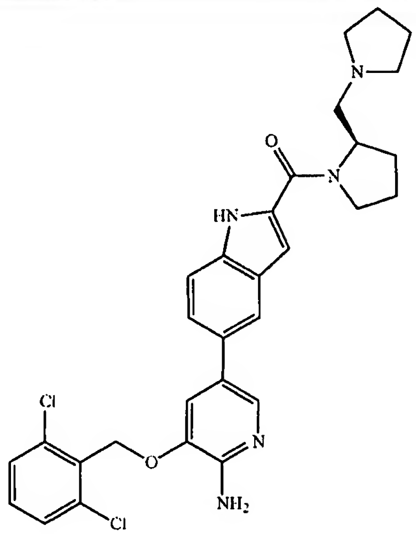
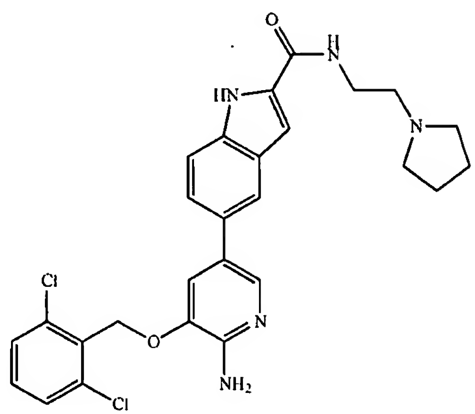
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-80		{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.079	see examples	(400 MHz, DMSO-d_6) δ 1.80(m, 1H), 2.12(m, 1H), 2.21(s, 6H), 2.74(m, 1H), 3.25(m, 1H), 3.53(m, 1H), 3.78(m, 1H), 4.02(m, 1H), 5.36(s, 2H), 5.54(s, 2H), 8.98(s, 1H), 7.46(m, 3H), 7.56(m, 3H), 7.88 (m, 2H), 11.53(s, 1H)	524
I-81		5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide	1.2	see examples	(400 MHz, DMSO-d_6) δ 1.68(m, 4H), 2.51 (m, 4H), 2.58(t, 2H), 3.39(m, 2H), 7.11(s, 1H), 7.45(m, 2H), 7.55(m, 3H), 7.60(m, 1H), 7.82(s, 1H), 7.88(s, 1H), 8.45(t, 1H), 11.56(s, 1H)	524

TABLE 2-continued

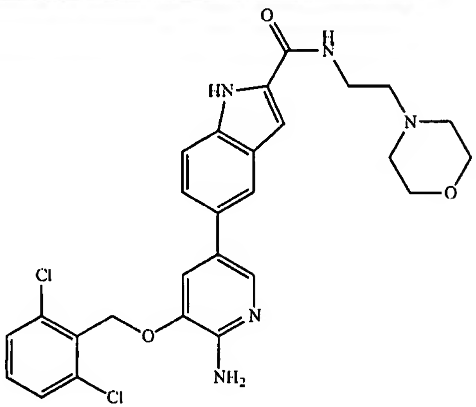
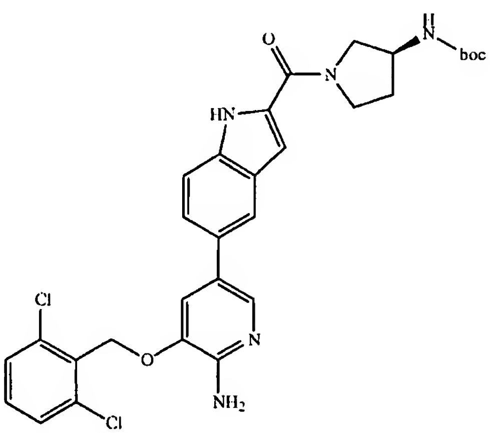
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-82		5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	1.8	see examples	(400 MHz, DMSO-d_6) δ 2.41(m, 6H), 3.39 (m, 2H), 3.58(m, 4H), 7.11(s, 1H), 7.45(m, 2H), 7.55(m, 4H), 7.82(s, 1H), 7.88(s, 1H), 8.42(t, 1H), 11.52(s, 1H)	540
I-83		(1-{5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carbonyl}--(3S)-pyrrolidin-3-yl)-carbamic acid tert-butyl ester	5	see examples	(400 MHz, DMSO-d_6) δ 1.38(s, 9H), 1.64(m, 1H), 1.98(m, 2H), 3.18(m, 2H), 3.78(m, 2H), 5.37(s, 2H), 5.53(s, 2H), 8.92(m, 1H), 7.26(m, 1H), 7.48(m, 2H), 7.56(m, 3H), 7.61(m, 1H), 7.86(m, 2H), 11.52(s, 1H)	596

TABLE 2-continued

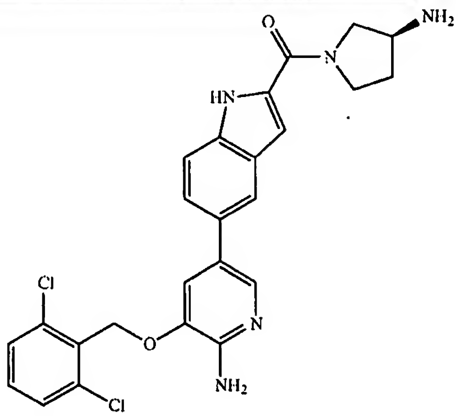
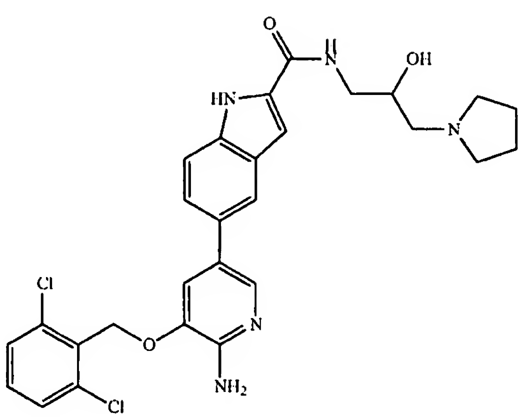
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-84		{5-(6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indol-2-yl}-[(3S)-amino-pyrrolidin-1-yl]-methanone	0.14	see examples	(400 MHz, DMSO-d_6) δ 2.20(m, 2H), 2.68 (m, 1H), 3.84(m, 4H), 5.58(s, 2H), 7.52(m, 6H), 7.94(m, 5H), 8.62(m, 2H)	496
I-85		5-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-1H-indole-2-carboxylic acid (2-hydroxy-3-pyrrolidin-1-yl-propyl)-amide	0.7	see examples	(400 MHz, DMSO-d_6) δ 1.87(m, 4H), 2.37 (m, 1H), 2.52(m, 1H), 3.31(m, 1H), 3.62(m, 4H), 3.46(m, 1H), 3.76(m, 1H), 5.38(s, 2H), 5.52(s, 2H), 7.14(s, 1H), 7.46(m, 2H), 7.56(m, 4H), 7.86(m, 2H), 8.48(t, 1H), 11.58(s, 1H)	554

TABLE 2-continued

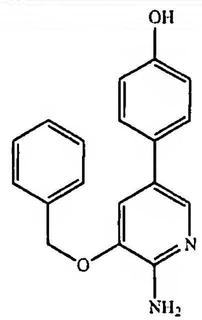
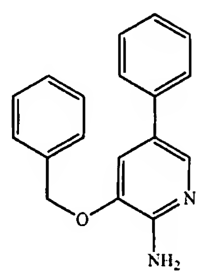
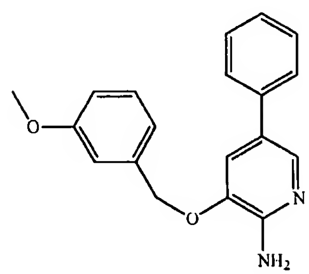
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-86		4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenol	8.7	see examples	(400 MHz, DMSO-d_6) δ 9.4 (s, 1H), 7.74 (d, J=2 Hz, 1H), 7.52 (d, J=7.2 Hz, 2H), 7.38 (m, 4H), 7.32 (m, 2H), 6.8(d, J=7.2 Hz, 2H), 5.69(s, 2H), 5.22(s, 2H)	293
I-87		3-Benzyloxy-5-phenyl-pyridin-2-ylamine		see examples	(400 MHz, DMSO-d_6) 7.84(d, 1H), 7.56(d, 2H), 7.51(d, 2H), 7.38(m, 5H), 7.31(t, 1H), 7.25(t, 1H), 5.83(br s, 2H), 5.24(s, 2H)	277
I-88		3-(3-Methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine		see examples	(400 MHz, DMSO-d_6) 7.85(d, 1H), 7.56(m, 2H), 7.38(m, 3H), 7.28(m, 2H), 7.08(m, 2H), 6.86(m, 1H), 5.84(br s, 2H), 5.21(s, 2H), 3.75(s, 3H)	307

TABLE 2-continued

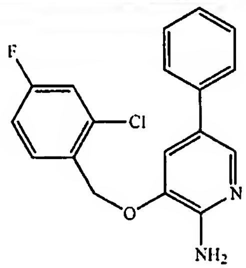
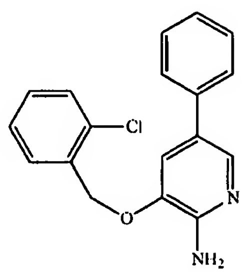
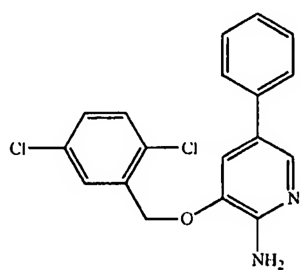
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-89		3-(2-Chloro-4-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	17	see examples	(400 MHz, DMSO-d_6) δ 7.88(s, 1H), 7.79(m, 1H), 7.59(m, 2H), 7.51(dd, 1H), 7.40(m, 3H), 7.27(m, 2H), 5.84(s, 2H), 5.24(s, 2H)	329
I-90		3-(2-Chloro-benzyloxy)-5-phenyl-pyridin-2-ylamine	48% at 20 uM	see examples	(400 MHz, DMSO-d_6) δ 7.68(d, 1H), 7.73(m, 1H), 7.68(m, 2H), 7.50(m, 1H), 7.38(m, 5H), 7.26(m, 1H), 5.57(s, 2H), 5.30(s, 2H)	311
I-91		3-(2,5-Dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine	48% at 20 uM	see examples	(400 MHz, DMSO-d_6) δ 7.89(d, 1H), 7.85(d, 1H), 7.59(m, 2H), 7.53(d, 1H), 7.46(d, 1H), 7.39(m, 3H), 7.26(m, 1H), 5.95(s, 2H), 5.30(s, 2H)	345

TABLE 2-continued

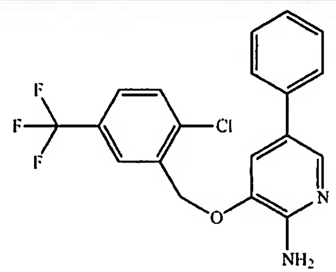
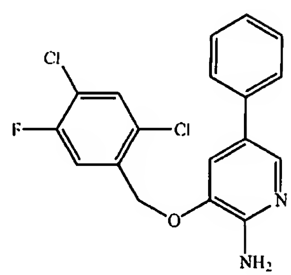
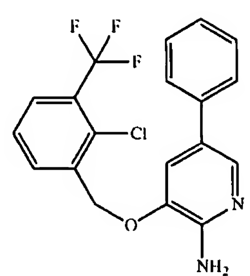
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-92		3-(2-Chloro-5-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine	>20	see examples	(400 MHz, DMSO-d_6) δ 8.15(s, 1H), 7.89(d, 1H), 7.76(d, 2H), 7.59(m, 2H), 7.48(d, 1H), 7.39(m, 2H), 7.26(m, 1H), 5.90(s, 2H), 5.36(s, 2H)	379
I-93		3-(2,4-Dichloro-5-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	>20	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.88(m, 2H), 7.60(m, 2H), 7.44(d, 1H), 7.39(m, 2H), 7.26(m, 1H), 6.01(s, 2H), 5.24(s, 2H)	364
I-94		3-(2-Chloro-3-trifluoromethyl-benzyloxy)-5-phenyl-pyridin-2-ylamine	>20	see examples	(400 MHz, DMSO-d_6) δ 8.10(d, 1H), 7.89(d, 1H), 7.85(m, 1H), 7.60(m, 3H), 7.45(d, 1H), 7.39(m, 2H), 7.26(m, 1H), 5.93(s, 2H), 5.37(s, 2H)	379

TABLE 2-continued

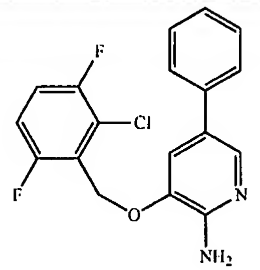
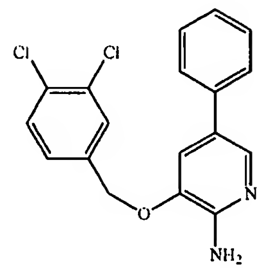
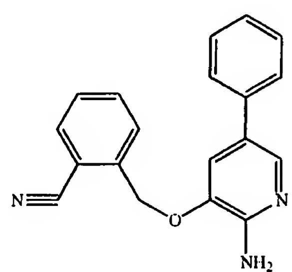
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-95		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	0.64	see examples	(400 MHz, DMSO-d_6) δ 7.89(d, 1H), 7.57(m, 4H), 7.40(m, 3H), 7.26(m, 1H), 5.72(s, 2H), 5.28(s, 2H)	347
I-96		3-(3,4-Dichloro-benzyloxy)-5-phenyl-pyridin-2-ylamine	16.2	see examples	(400 MHz, DMSO-d_6) δ 7.86(d, 1H), 7.84(d, 1H), 7.65(m, 1H), 7.67(m, 3H), 7.39(m, 3H), 7.26(m, 1H), 5.96(s, 2H), 5.24(s, 2H); MS m/z 345 [M + 1].	345
I-97		2-(2-Amino-5-phenyl-pyridin-3-yloxymethyl)-benzonitrile	12.2	see examples	(400 MHz, DMSO-d_6) δ 7.90(dd, 2H), 7.82(d, 1H), 7.75(m, 1H), 7.56(m, 3H), 7.48(d, 1H), 7.40(m, 2H), 7.26(m, 1H), 5.85(s, 2H), 5.39(s, 2H)	302

TABLE 2-continued

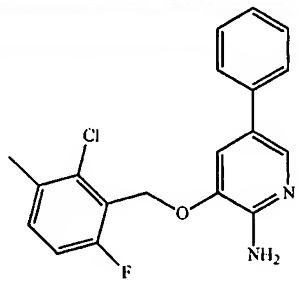
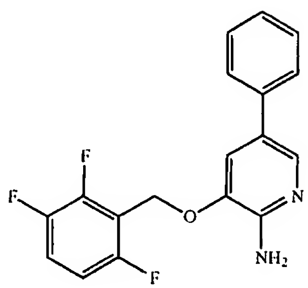
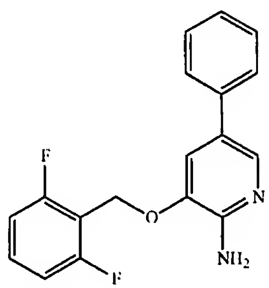
No.	Structure	Name	Met IC_{50} (µM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-98		3-(2-Chloro-6-fluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine	7.6	see examples	(400 MHz, DMSO-d_6) δ 7.88(d, 1H), 7.61(m, 2H), 7.53(d, 1H), 7.43(m, 3H), 7.25(m, 2H), 5.65(s, 2H), 5.27(s, 2H), 2.34(s, 3H)	342
I-99		5-Phenyl-3-(2,3,6-trifluoro-benzyloxy)-pyridin-2-ylamine	3.9	see examples	(400 MHz, DMSO-d_6) δ 7.89(d, 1H), 7.61(m, 3H), 7.52(d, 1H), 7.40(m, 2H), 7.25(m, 2H), 5.75(s, 2H), 5.26(s, 2H)	331
I-100		3-(2,6-Difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	9.3	see examples	(400 MHz, DMSO-d_6) δ 7.88(d, 1H), 7.61(m, 2H), 7.51(m, 2H), 7.40(m, 2H), 7.26(m, 1H), 7.18(m, 2H), 5.69(s, 2H), 5.23(s, 2H)	314

TABLE 2-continued

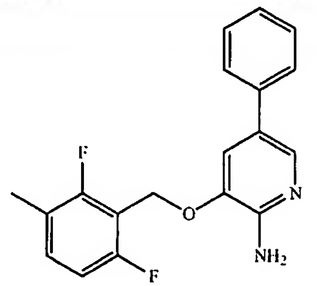
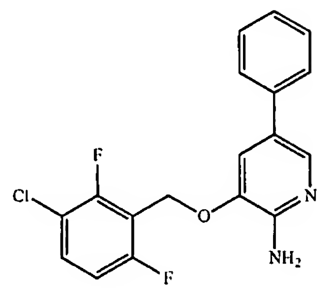
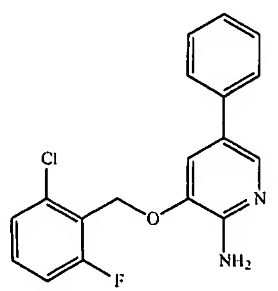
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-101		3-(2,6-Difluoro-3-methyl-benzyloxy)-5-phenyl-pyridin-2-ylamine	12	see examples	(400 MHz, DMSO-d_6) δ 7.88(d, 1H), 7.60(m, 2H), 7.51(d, 1H), 7.40(m, 3H), 7.27(m, 1H), 7.07(m, 1H), 5.68(s, 2H), 5.21(s, 2H)	328
I-102		3-(3-Chloro-2,6-difluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	9.6	see examples	(400 MHz, DMSO-d_6) δ 7.88(d, 1H), 7.74(m, 1H), 7.61(m, 2H), 7.51(d, 1H), 7.40(m, 2H), 7.27(m, 2H), 5.76(s, 2H), 5.26(s, 2H)	347
I-103		3-(2-Chloro-8-fluoro-benzyloxy)-5-phenyl-pyridin-2-ylamine	7.91	see examples	(400 MHz, DMSO-d_6) δ 7.88(d, 1H), 7.61(m, 2H), 7.52(d, 1H), 7.49(m, 1H), 7.40(m, 3H), 7.30(m, 2H), 5.67(s, 2H), 5.27(s, 2H)	329

TABLE 2-continued

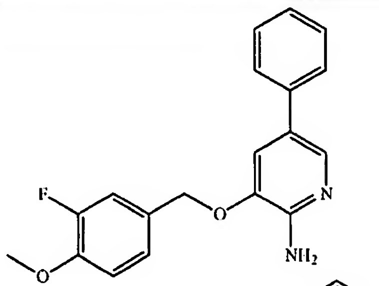
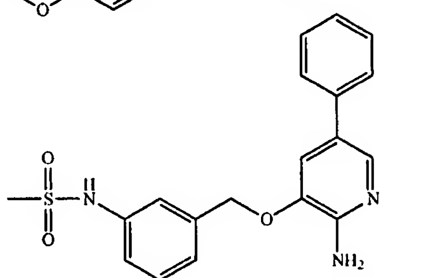
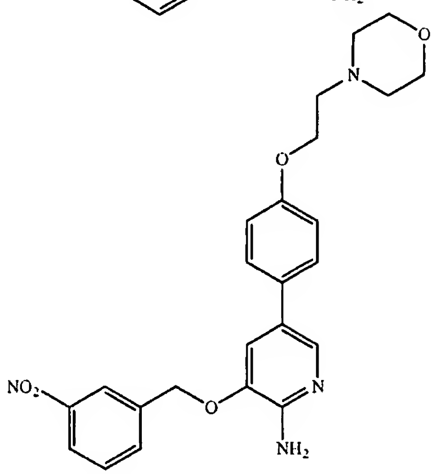
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-104		3-(3-Fluoro-4-methoxy-benzyloxy)-5-phenyl-pyridin-2-ylamine	15	see examples	(400 MHz, DMSO-d_6) δ 7.84(d, 1H), 7.56(m, 1H), 7.43(d, 1H), 7.38(m, 3H), 7.26(m, 2H), 7.10(m, 2H), 5.58(s, 2H), 5.15(s, 2H)	325
I-105		N-[3-(2-Amino-5-phenyl-pyridin-3-yloxymethyl)-phenyl]-methanesulfonamide	>20	see examples	(400 MHz, DMSO-d_6) δ 9.76(s, 1H), 7.85(d, J=1.8 Hz, 1H), 7.57(d, 2H), 7.38(m, 5H), 7.28(m, 2H), 7.15(d, 1H), 5.85(br s, 2H), 5.22(s, 2H), 2.96(s, 3H)	370
I-106		5-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-3-(3-nitro-benzyloxy)-pyridin-2-ylamine	12.6	see examples	(DMSO-d_6) δ 2.50(m, 4H), 2.69(m, 2H), 3.57(t, 4H), 4.09(t, 2H), 5.37 (s, 2H), 5.85(s, 2H), 6.96(d, 2H), 7.38(d, 1H), 7.48(d, 2H), 7.69(t, 1H), 7.81(d, 1H), 8.01(m, 1H), 8.17(m, 1H), 8.36(m, 1H)	451

TABLE 2-continued

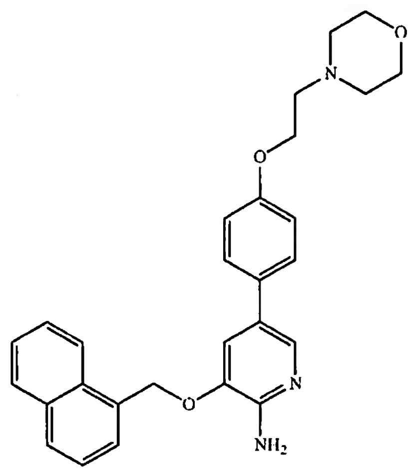
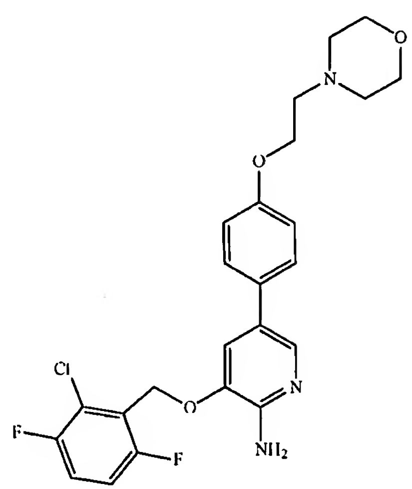
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-107		5-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-3-(naphthalen-1-ylmethoxy)-pyridin-2-ylamine	7.7	see examples	(DMSO-d_6) δ 2.50(m, 4H), 2.69(t, 2H), 3.57(t, 4H), 4.10(t, 2H), 5.66 (s, 2H), 5.67(s, 2H), 6.97(d, 2H), 7.49–7.61(m, 5H), 7.78–7.82(m, 2H), 7.88–7.98(m, 2H), 8.20(dd, 1H)	456
I-108		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.21	see examples	(400 MHz, $CDCl_3$) δ 2.60(m, 4H), 2.83(t, 2H), 3.74(t, 4H), 4.16(t, 2H), 4.63 (s, 2H), 5.27(d, 2H), 6.98(d, 2H), 7.02–7.10(m, 1H), 7.16–7.22(m, 1H), 7.30(2, 2H), 7.44(d, 2H), 7.91(d, 1H)	476

TABLE 2-continued

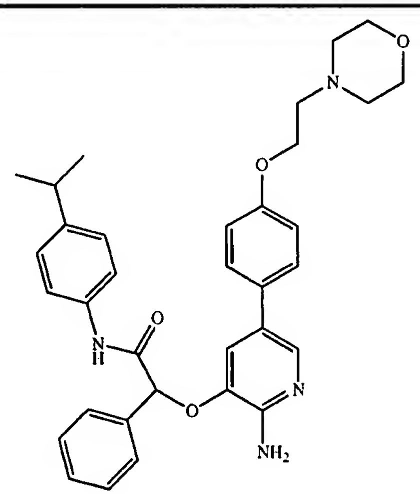
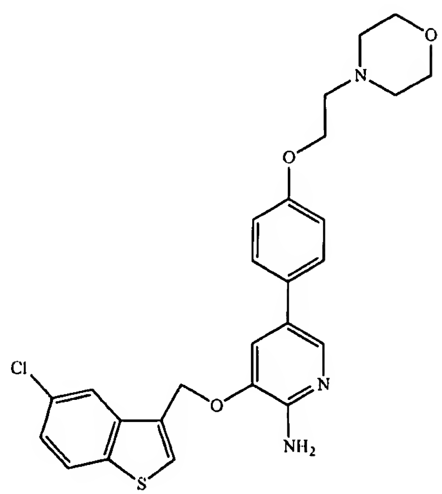
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-109		2-{2-Amino-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-3-yloxy}-N-(4-isopropyl-phenyl)-2-phenyl-acetamide	>20	see examples	(400 MHz, DMSO-d_6) δ 1.15(d, 6H), 2.50(m, 4H), 2.68(m, 2H), 2.77–2.89(m, 1H), 3.57(t, 6H), 4.08(t, 2H), 6.15(s, 1H), 6.20(s, 2H), 6.93(d, 2H), 7.17(d, 1H), 7.30–7.44(m, 3H), 7.48(d, 2H), 7.68(d, 2H), 7.79(d, 1H)	568
I-110		3-(5-Chloro-benzo[b]thiophen-3-ylmethoxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	2.4	see examples	(400 MHz, DMSO-d_6) δ 2.50(m, 4H), 2.70(m, 2H), 3.58(t, 4H), 4.11(t, 2H), 5.46 (s, 2H), 5.82(s, 2H), 6.98(d, 2H), 7.43 (dd, 1H), 7.50–7.56(m, 3H) 7.80(d, 1H), 8.05(d, 1H), 8.11(d, 1H), 8.16(s, 1H)	496.5

TABLE 2-continued

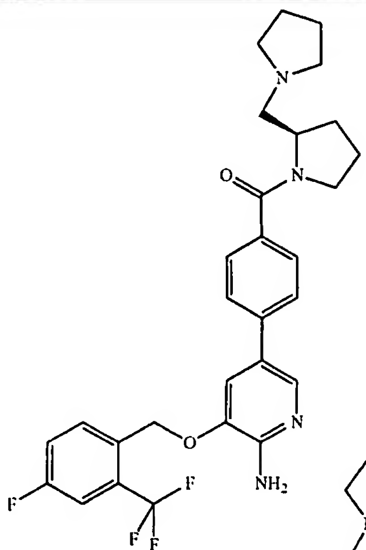
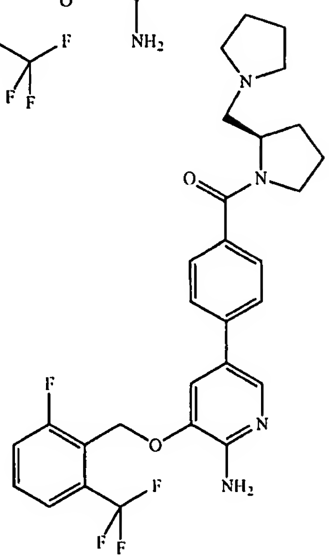
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-111		{4-[6-Amino-5-(4-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.51	see examples	(400 MHz, DMSO-d_6) δ 7.94(s, 2H), 7.71(m, 4H), 7.44(m, 3H), 5.92(s, 2H), 5.36(s, 2H), 4.21(m, 1H), 3.52(m, 2H), 2.69(m, 5H), 1.96(m, 2H), 1.84(m, 3H), 1.68(m, 4H)	543
I-112		{4-[6-Amino-5-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.15	see examples	(400 MHz, DMSO-d_6) δ 7.94(s, 1H), 7.69(m, 5H), 7.59(s, 1H), 7.50(m, 2H), 5.72(s, 2H), 5.26(s, 2H), 4.16(m, 1H), 3.47(m, 2H), 2.63(m, 5H), 1.96(m, 2H), 1.86(m, 3H), 1.68(m, 4H)	543

TABLE 2-continued

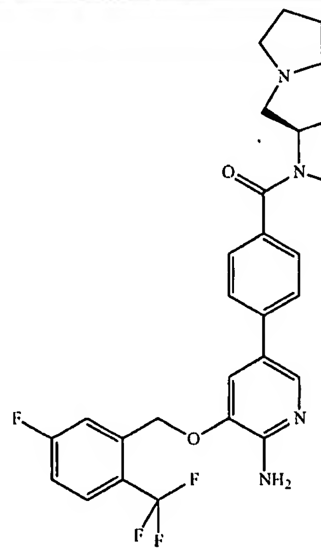
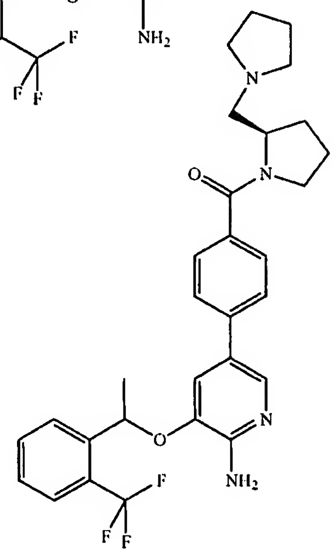
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-113		{4-(6-Amino-5-(5-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.27	see examples	(400 MHz, DMSO-d_6) δ 7.95(s, 1H), 7.85(m, 2H), 7.63(m, 2H), 7.48(m, 2H), 7.42(m, 2H), 6.04(s, 2H), 5.36(s, 2H), 4.16(m, 1H), 3.44(m, 2H), 2.62(m, 5H), 1.96(m, 2H), 1.85(m, 3H), 1.66(m, 4H)	543
I-114		(4-{6-Amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.33	see examples	(400 MHz, DMSO-d_6) δ 7.85(d, 1H), 7.81(s, 1H), 7.76(m, 2H), 7.41(m, 5H), 7.03(s, 1H), 6.16(s, 2H), 5.81(m, 1H), 4.10(m, 1H), 3.41(m, 2H), 2.59(m, 5H), 1.94(m, 2H), 1.82(m, 3H), 1.64(d, 3H), 1.48(m, 4H)	539

TABLE 2-continued

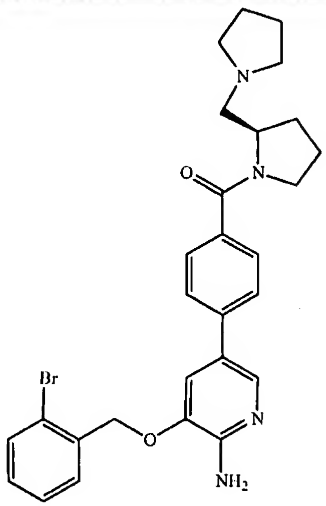
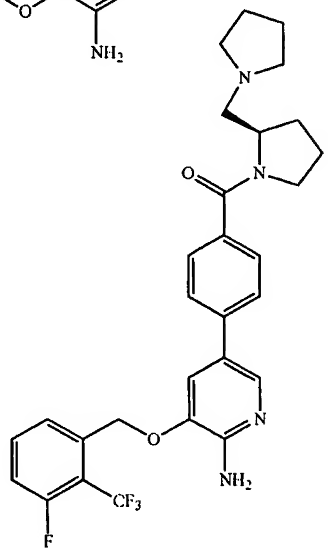
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-115		{4-[6-Amino-5-(2-bromo-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.75	see examples	(400 MHz, DMSO-d_6) δ 7.74(s, 1H), 7.68(m, 3H), 7.45(m, 5H), 7.31(m, 1H), 5.92(s, 2H), 5.25(s, 2H), 4.16(m, 1H), 3.43(m, 2H), 2.62(m, 5H), 1.94(m, 2H), 1.82(m, 3H), 1.65(m, 4H)	537
I-116		{4-(6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.025	see examples	(400 MHz, DMSO-d_6) δ 7.92(s, 1H), 7.66(m, 4H), 7.46(m, 4H), 5.89(s, 2H), 5.39(s, 2H), 4.19(m, 1H), 3.50(m, 2H), 2.54(m, 5H), 1.95(m, 2H), 1.83(m, 3H), 1.64(m, 4H)	543

TABLE 2-continued

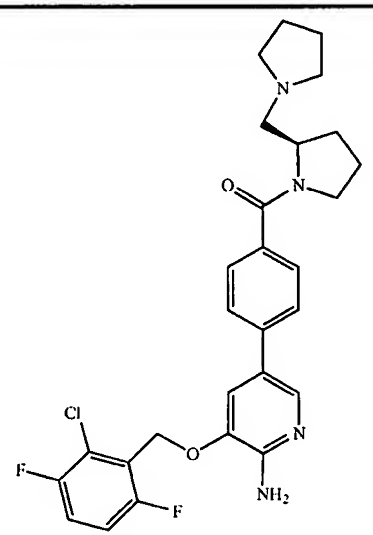
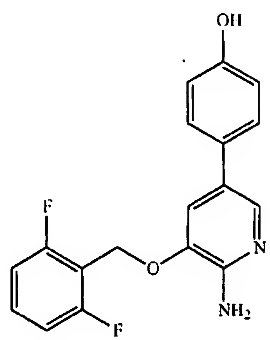
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-117		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.063	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.69(d, 2H), 7.58(m, 2H), 7.50(d, 2H), 7.40(m, 1H), 5.81(s, 2H), 5.29(s, 2H), 4.35(m, 1H), 3.5(d, 2H), 2.87(d, 2H), 2.71(d, 2H), 1.7–2.0(m, 10H)	527
I-118		4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl	3.79	see examples	(400 MHz, DMSO-d_6) δ 9.38(s, 1H), 7.77(d, J=2 Hz 1H), 7.52(m, 2H), 7.40(m, 3H), 7.17(m, 2H), 6.79(m, 2H), 5.53(br. s, 2H), 5.20(s, 2H)	329

TABLE 2-continued

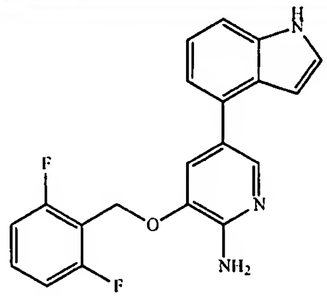
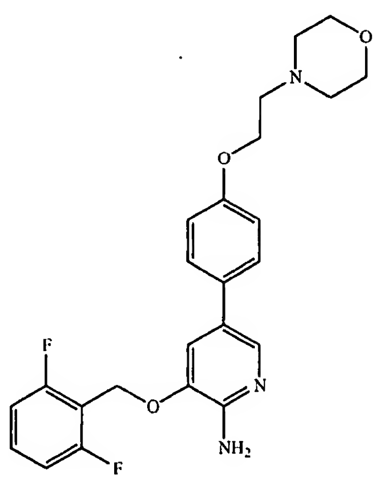
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-119		3-(2,6-Difluoro-benzyloxy)-5-(1H-indol-4-yl)-pyridin-2-ylamine	5.8	see examples	(400 MHz, DMSO-d_6) δ 7.81(d, J=2 Hz, 1H), 7.51(m, 3H), 7.45(d, J=2 Hz, 1H), 7.17(m, 2H), 6.98 (m, 2H), 5.58(s, 2H), 5.21(s, 2H), 4.10(t, 2H), 3.57(t, 4H), 2.69(t, 2H), 2.48(t, 4H)	442
I-120		3-(2,6-Difluoro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine		see examples	(400 MHz, DMSO-d_6) δ 11.18(s, 1H), 7.86(d, J=2 Hz, 1H), 7.52 (m, 1H), 7.44(d, J=2 Hz, 1H), 7.36(dd, 1H), 7.34(m, 1H), 7.18(m, 2H), 7.13(dd, 1H), 7.02(dd, 1H), 6.49(m, 1H), 5.66(s, 2H), 5.22(s, 2H)	352

TABLE 2-continued

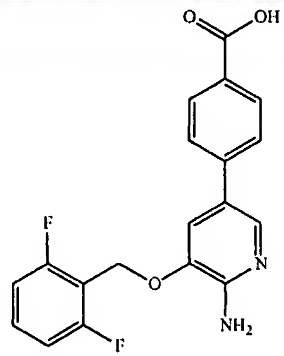
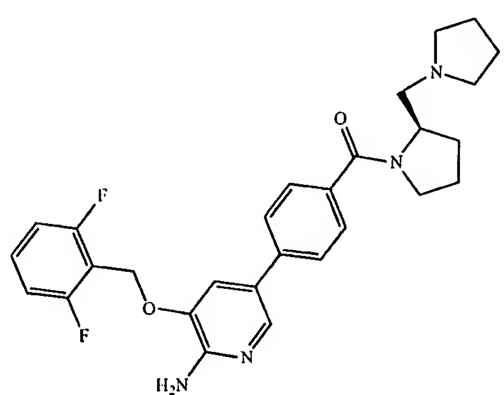
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-121		4-(6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 12.85(s, 1H), 7.94(d, J=2 Hz, 1H), 7.89 (dd, 2H), 7.71(dd, 2H), 7.55(d, J=2 Hz, 1H), 7.47(m, 1H), 7.13(m, 2H), 5.83(s, 2H), 5.19(s, 2H)	357
I-122	Chiral 	{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.21	see examples	(400 MHz, DMSO-d_6) δ 7.94(d, 1H), 7.68(dd, 2H), 7.56(m, 1H), 7.51(m, 3H), 7.18(m, 2H), 5.79 (s, 2H), 5.29(s, 2H), 3.48(m, 1H), 2.65(m, 4H), 2.48(d, 2H), 1.86(m, 10H)	493

TABLE 2-continued

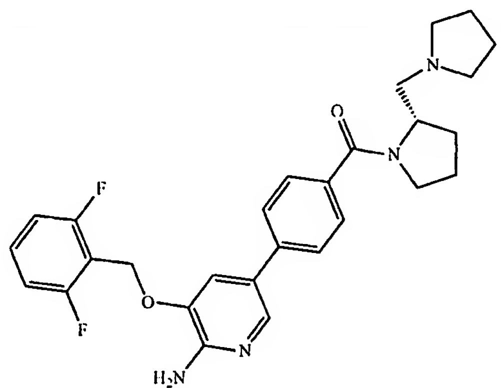
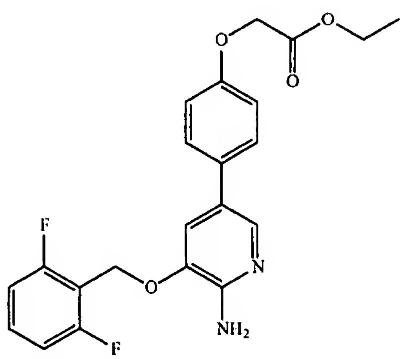
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-123	 Chiral	{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.36	see examples	(400 MHz, DMSO-d_6) δ 7.94(d, 1H), 7.68(dd, 2H), 7.56(m, 1H), 7.51(m, 3H), 7.18(m, 2H), 5.78 (s, 2H), 5.24(s, 2H), 4.8(m, 1H), 3.5(m, 2H), 2.52(d, 4H), 1.86(m, 10H)	493
I-124		{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid ethyl ester		see examples	(400 MHz, DMSO-d_6) δ 7.81(d, J=2 Hz, 1H), 7.52(m, 3H), 7.18(m, 1H), 6.96(m, 2H), 5.70(br. s, 2H), 5.23(s, 2H), 4.79(s, 2H), 2.68(q, 4H), 1.21(t, 3H)	415

TABLE 2-continued

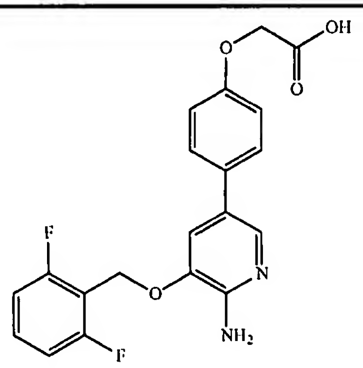
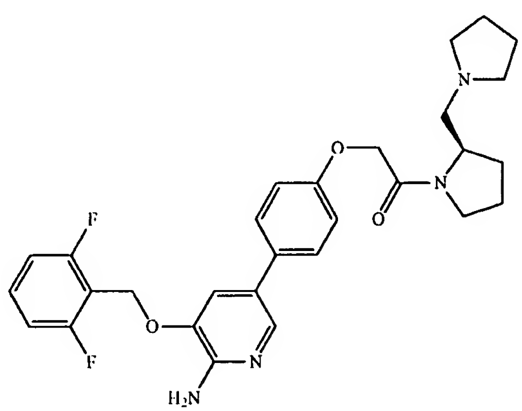
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-125		{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-acetic acid	14.7	see examples	(400 MHz, DMSO-d_6) δ 7.79(d, 1H), 7.51(m, 1H), 7.47(m, 1H), 7.44 (m, 2H), 7.17(m, 2H), 7.05(m, 2H), 5.55(br. s, 2H), 5.21(s, 2H), 4.25(s, 2H)	387
I-126	 Chiral	2-{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone	3.58	see examples	(400 MHz, DMSO-d_6) δ 7.81(d, 1H), 7.51(m, 3H), 7.45(d, 1H), 7.18 (m, 2H), 6.80(m, 2H), 5.65(s, 2H), 5.22(s, 2H), 4.80(dd, 2H), 4.29(m, 1H), 3.53(m, 2H), 3.20(m, 4H), 1.93(m, 10H)	523

TABLE 2-continued

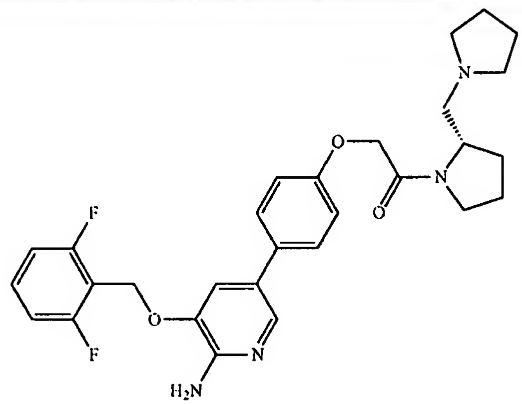
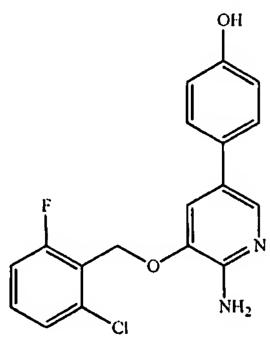
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-127	 Chiral	2-{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenoxy}-1-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-ethanone	5.43	see examples	(400 MHz, DMSO-d_6) δ 7.81(d, 1H), 7.52(m, 3H), 7.46(d, 1H), 7.18 (m, 2H), 7.00(m, 2H), 5.68(s, 2H), 5.22(s, 2H), 4.80(dd, 2H), 4.60(m, 1H), 3.53(m, 2H), 3.19(m, 4H), 1.96(m, 10H)	523
I-128		4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenol	3.99	see examples	(400 MHz, DMSO-d_6) δ 9.38(s, 1H), 7.77(d, 1H), 7.50(m, 1H), 7.42 (m, 4H), 7.39(m, 1H), 6.80(m, 2H), 5.50(s, 2H), 5.24(s, 2H)	345

TABLE 2-continued

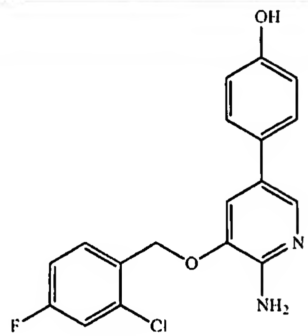
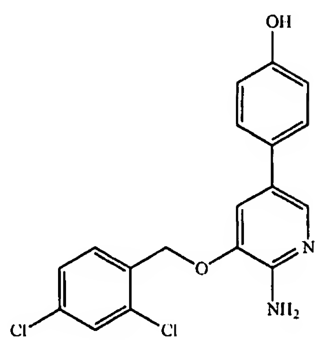
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-129		4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenol	19	see examples	(DMSO-d_6) δ 5.21(s, 2H), 5.67(s, 2H), 6.80(d, 2H), 7.26(t, 1H), 7.34(s, 1H), 7.41(d, 2H), 7.50(d, 1H), 7.79(m, 2H), 9.38(s, 1H)	345
I-130		4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenol	9/>20	see examples	(DMSO-d_6) δ 5.21(s, 2H), 5.71(s, 2H), 6.81(d, 2H), 7.40(m, 5H), 7.74(m, 2H), 9.38(s, 1H)	361

TABLE 2-continued

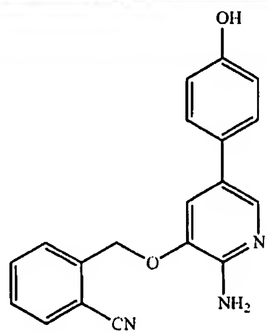
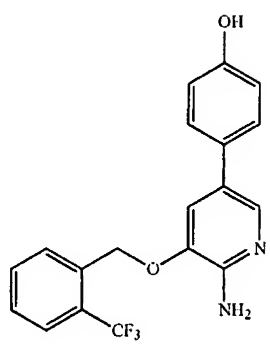
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-131		2-[2-Amino-5-(4-hydroxy-phenyl)-pyridin-3-yloxymethyl]-benzonitrile	19	see examples	(DMSO-d_6) δ 5.35(s, 2H), 5.68(s, 2H), 6.77(d, 2H), 7.41(m, 3H), 7.54(t, 1H), 7.78(m, 3H), 7.92(d, 1H), 9.38(s, 1H)	318
I-132		4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenol	3.67	see examples	(400 MHz, DMSO-d_6) δ 5.32(s, 2H), 5.68(s, 2H), 6.78(d, 2H), 7.26(s, 1H), 7.36(d, 2H), 7.57(t, 1H), 7.72(t, 1H), 7.78(m, 2H), 7.86(m, 1H), 9.38(s, 1H)	361

TABLE 2-continued

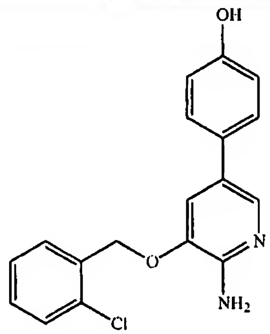
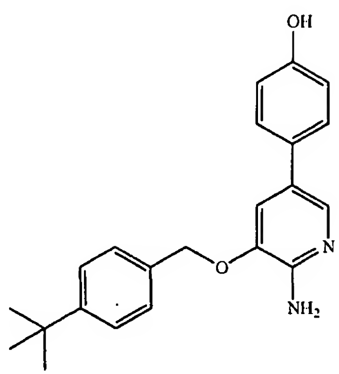
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-133		4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenol	13.8	see examples	(DMSO-d_6) δ 5.25(s, 2H), 5.69(s, 2H), 6.78(d, 2H), 7.38(m, 5H), 7.50(m, 1H), 7.71(m, 1H), 7.78(s, 1H), 9.38(s, 1H)	326
I-134		4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenol	4	see examples	(DMSO-d_6) δ 1.26(s, 9H), 5.16(s, 2H), 5.63(s, 2H), 6.78(d, 2H), 7.40(m, 7H), 7.72(s, 1H), 9.36(s, 1H)	349

TABLE 2-continued

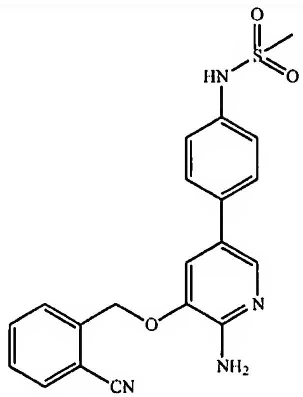
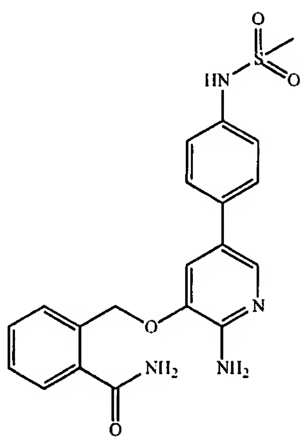
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-135		N-{4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide	4.18	see examples	(DMSO-d_6) δ 2.98(s, 3H), 5.36(s, 2H), 5.82(s, 2H), 7.24(d, 2H), 7.42(s, 1H), 7.58(m, 3H), 7.75(t, 1H), 7.89(m, 3H), 9.70(s, 1H)	393
I-136		2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzamide	>20	see examples	(DMSO-d_6) δ 2.88(s, 3H), 5.37(s, 2H), 5.75(s, 2H), 7.15(d, 2H), 7.30(s, 1H), 7.48(m, 6H), 7.20(d, 1H), 7.80(s, 1H), 7.90(s, 1H)	413

TABLE 2-continued

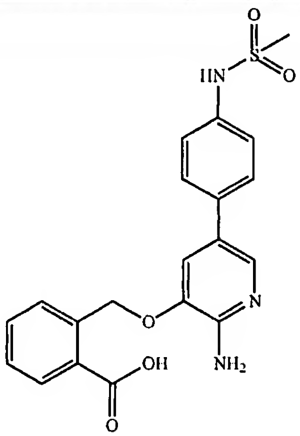
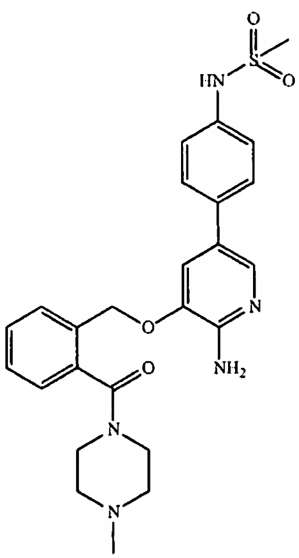
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-137		2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-benzoic acid	>20	see examples	(DMSO-d_6) δ 3.00(s, 3H), 5.65(s, 2H), 7.26(d, 2H), 7.47(m, 3H), 7.60(m, 4H), 7.72(m, 1H), 7.82(s, 1H), 7.94(d, 1H), 9.84(s, 1H)	414
I-138		N-(4-{6-Amino-5-[2-(4-methyl-piperazine-1-carbonyl)-benzyloxy]-pyridin-3-yl}-phenyl)-methanesulfonamide	>20	see examples	(DMSO-d_6) δ 2.08(s, 3H), 2.26(m, 2H), 2.96(s, 3H), 3.15(m, 2H), 3.36(m, 2H), 3.59(m, 2H), 5.17(br s, 2H), 5.78(s, 2H), 7.23(d, 2H), 7.28(m, 1H), 7.36(s, 1H), 7.43(m, 2H), 7.57(m, 4H), 7.84(s, 1H)	496

TABLE 2-continued

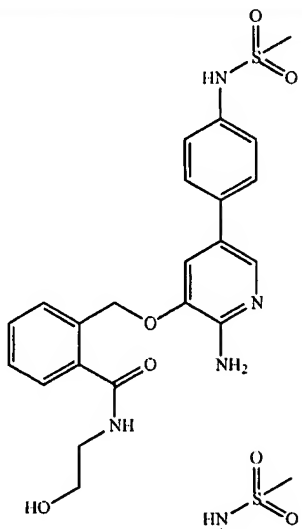
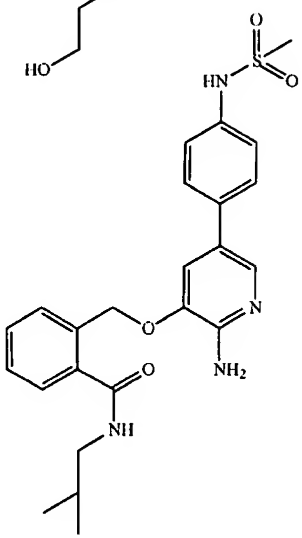
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-139		2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-N-(2-hydroxy-ethyl)-benzamide	>20	see examples	($DMSO-d_6$) δ 2.96(s, 3H), 3.28(m, 2H), 3.46(m, 2H), 4.70(s, 1H), 5.30(s, 2H), 5.78(s, 2H), 7.23(d, 2H), 7.32(s, 1H), 7.39(m, 1H), 7.47(m, 2H), 7.53(m, 2H), 7.62(d, 1H), 7.83(s, 1H), 8.37(t, 1H), 9.72(br s, 1H)	457
I-140		2-[2-Amino-5-(4-methanesulfonylamino-phenyl)-pyridin-3-yloxymethyl]-N-isobutyl-benzamide	>20	see examples	($DMSO-d_6$) δ 0.84(d, 6H), 1.78(m, 1H), 2.82(s, 3H), 3.03(t, 2H), 5.28(s, 2H), 5.72(s, 2H), 7.12(d, 2H), 7.24(s, 1H), 7.42(m, 5H), 7.62(d, 1H), 7.79(s, 1H), 8.41(t, 1H), 9.68(s, 1H)	469

TABLE 2-continued

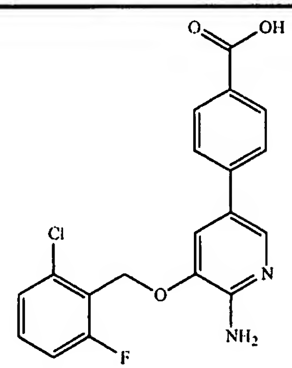
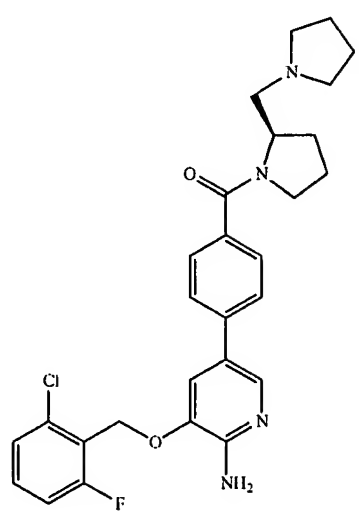
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-141		4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.25(s, 2H, CH_2), 5.82(br s, 2H, NH_2), 6.30–8.00(multiplets, 9H, aromatic)	373
I-142		{4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.63	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, 1H), 7.57(m, 4H), 7.10(m, 3H), 7.04(t, 1H), 5.30(s, 2H), 4.83(s, 2H), 4.45(m, 1H), 3.40(m, 2H), 2.90(m, 4H), 2.2–1.5(m, 10H)	509

TABLE 2-continued

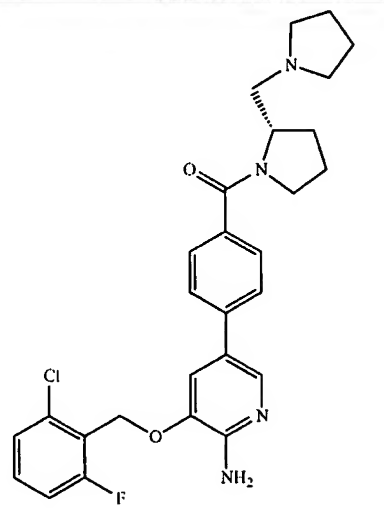
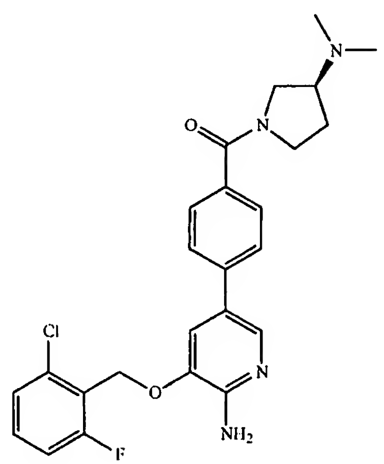
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-143		{4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	13	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, 1H), 7.57(m, 4H), 7.10(m, 3H), 7.04(t, 1H), 5.30(s, 2H), 4.83(s, 2H), 4.45(m, 1H), 3.40(m, 2H), 2.90(m, 4H), 2.2–1.5(m, 10H)	509
I-144		{4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	1.7	see examples	(300 MHz, $CDCl_3$) δ 7.94(s, 1H), 7.58(m, 4H), 7.36(m, 3H), 7.05(t, 1H), 5.30(s, 2H), 5.07(s, 2H), 3.9(m, 1H), 3.6(m, 2H), 3.4(m, 1H), 3.0(m, 1H), 2.37(s, 3H), 2.27(s, 3H), 1.8(m, 2H)	470

TABLE 2-continued

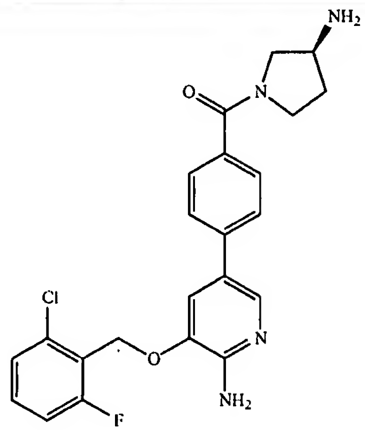
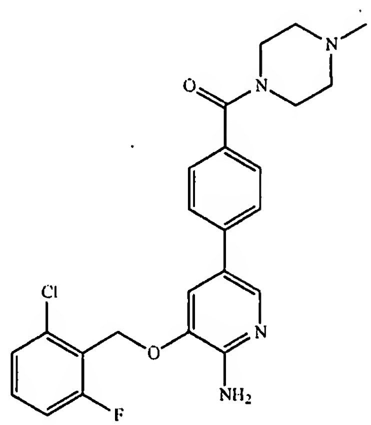
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-145		{4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	0.63	see examples		441
I-146		{4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	1.94	see examples	(300 MHz, $CDCl_3$) δ 7.93(d, J=1.7 Hz, 1H), 7.56(d, J=8.1 Hz, 2H), 7.48(d, J=8.1 Hz, 2H), 7.28(m, 3H), 7.07(t, J=8.8 Hz), 5.30(s, 2H), 5.05(br s, 2H), 375(m, 4H), 2.48(m, 4H), 2.34(s, 3H)	455

TABLE 2-continued

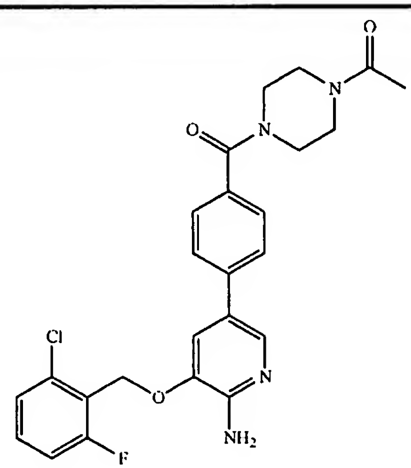
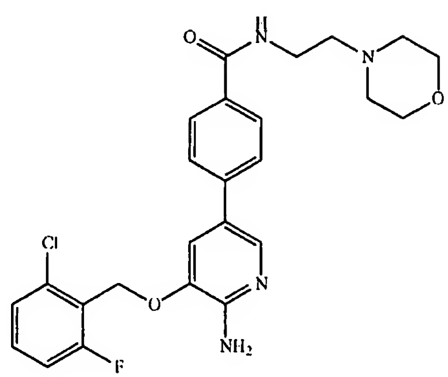
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-147		1-(4-{4-(6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	1.45	see examples	(300 MHz, $CDCl_3$) δ 7.91(d, J=1.7 Hz, 1H), 7.58(d, J=8.2 Hz, 2H), 7.50(d, J=8.2 Hz, 2H), 7.35(m, 3H), 7.08(t, J=8.2 Hz), 5.42(br s, 2H), 5.32(s, 2H), 3.60(m, 8H), 2.14(s, 3H)	484
I-148		4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	6.4	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.85(d, J=8.2 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H), 7.30(m, 2H), 7.24(d, J=1.7 Hz, 1H), 7.08(m, 1H), 6.95(br t, 1H), 5.32(s, 2H), 5.06(br s, 2H), 3.82(m, 4H), 3.64(m, 2H), 2.76(m, 2H), 2.65(m, 4H)	485

TABLE 2-continued

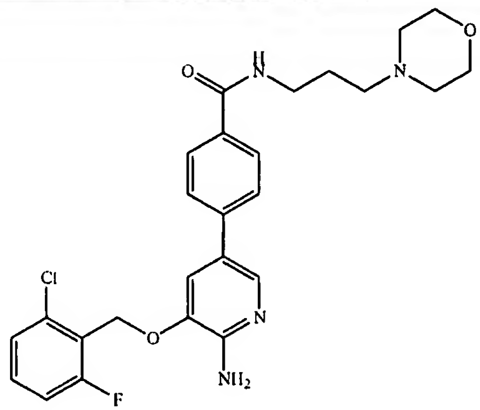
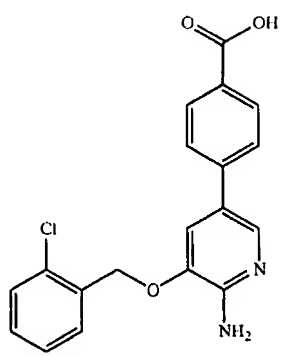
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-149		4-[6-Amino-5-(2-chloro-6-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	5.6	see examples	(300 MHz, $CDCl_3$) δ 8.02(br t, 1H), 7.95(d, J=1.7 Hz, 1H), 7.90(d, J=8.3 Hz, 2H), 7.59(d, J=8.3 Hz, 2H), 7.39(d, J=1.7 Hz, 1H), 7.30(m, 2H), 7.08(m, 1H), 6.95(br t, 1H), 5.32(s, 2H), 5.10(br s, 2H), 3.78(m, 4H), 3.62(m, 2H), 2.64(m, 6H), 1.87(m, 2H)	499
I-150		4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.30(s, 2H, CH_2), 5.95(br s, 2H, NH_2), 7.35-7.95(multiplets, 10H, aromatic).	353 (M − 1)

TABLE 2-continued

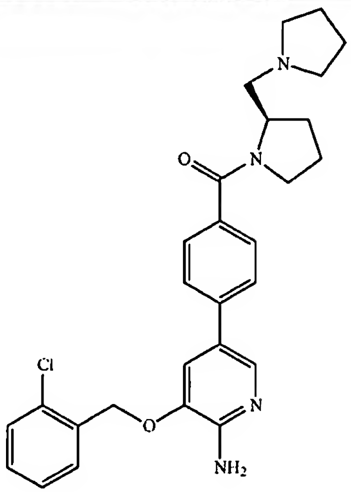
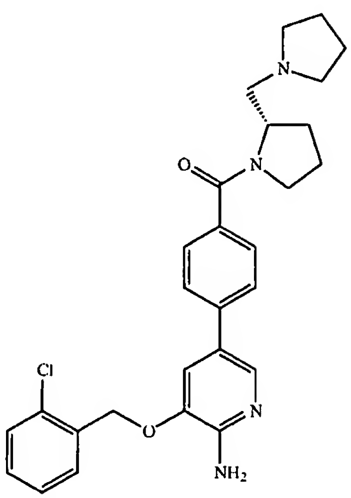
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-151		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.87	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.6 Hz, 1H), 7.52(m, 6H), 7.25(m, 2H), 7.21(d, J=1.6 Hz, 1H), 5.26(s, 2H), 4.88(br s, 2H), 4.32(m, 1H), 3.52(m, 2H), 2.89(m, 4H), 2.2–1.5(m, 10H).	491
I-152		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	2.3	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.6 Hz, 1H), 7.52(m, 6H), 7.25(m, 2H), 7.21(d, J=1.6 Hz, 1H), 5.26(s, 2H), 4.88(br s, 2H), 4.32(m, 1H), 3.52(m, 2H), 2.89(m, 4H), 2.2–1.5(m, 10H). MS m/z 491 [M + 1].	491

TABLE 2-continued

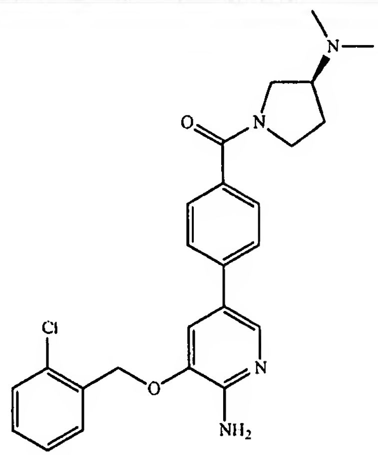
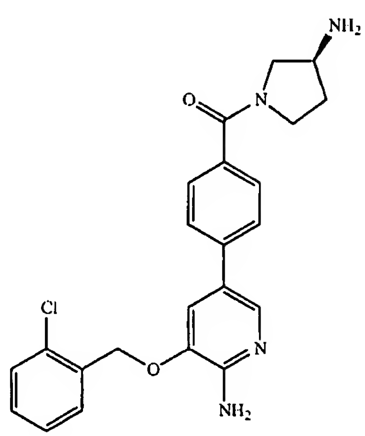
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-153		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	12.7	see examples	(300 MHz, $CDCl_3$) δ 7.95(s, 1H), 7.53(m, 6H), 7.33(m, 2H), 7.27(s, 1H), 5.26(s, 2H), 4.94(br s, 2H), 3.90(m, 1H), 3.60(m, 2H), 3.45(m, 1H), 2.85(m, 1H), 2.32(s, 3H), 2.23(s, 3H), 1.89(m, 2H)	451
I-154		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	1.44	see examples		423

TABLE 2-continued

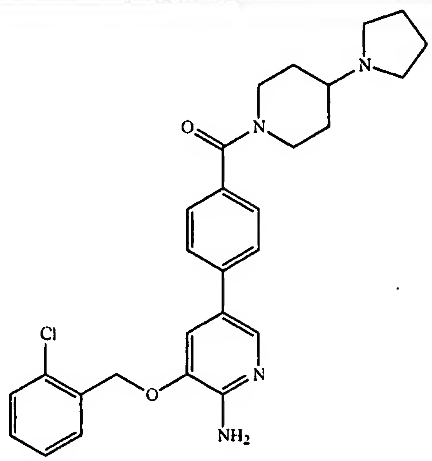
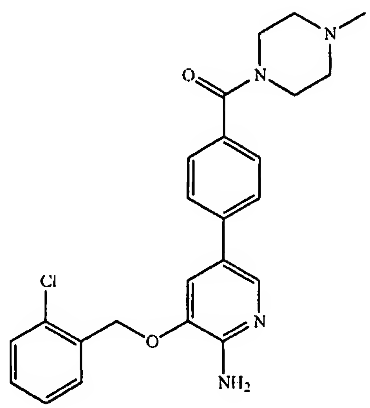
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-155		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	1.5	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.47(m, 6H), 7.32(m, 2H), 7.21(d, J=1.8 Hz, 1H), 5.26(s, 2H), 4.86(br s, 2H), 3.95(m, 4H), 2.55(m, 4H), 2.30(m, 1H), 1.95(m, 2H), 1.76(m, 4H), 1.52(m, 2H).	491
I-156		{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	2.1	see examples	(300 MHz, $CDCl_3$) δ 7.94(d, J=1.8 Hz, 1H), 7.49(m, 6H), 7.32(m, 2H), 7.21(d, J=1.8 Hz, 1H), 5.27(s, 2H), 4.00(br s, 2H), 3.80(m, 4H), 2.50(m, 4H), 2.35(s, 3H)	437

TABLE 2-continued

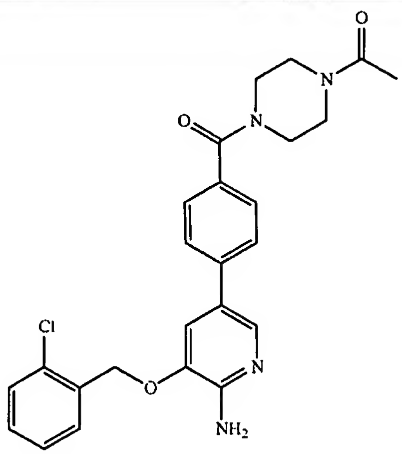
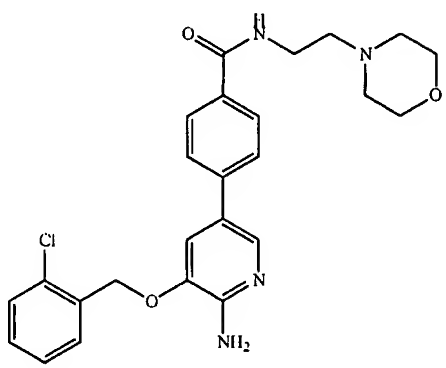
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-157		1-(4-{4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	3.8	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.51(m, 6H), 7.33(m, 2H), 7.21(d, J=1.8 Hz, 1H), 5.27(s, 2H), 4.94(br s, 2H), 3.65(m, 8H), 2.14(s, 3H)	465
I-158		4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	8.9	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.84(d, J=8.3 Hz, 2H), 7.55(d, J=8.3 Hz, 2H), 7.51(m, 1H), 7.43(m, 1H), 7.34(m, 2H), 7.24(d, J=1.8 Hz, 1H), 7.01(br t, 1H), 5.27(s, 2H), 5.18(br s, 2H), 3.77(m, 4H), 3.61(m, 2H), 3.25(m, 2H), 2.70(m, 2H), 2.60(m, 4H)	467

TABLE 2-continued

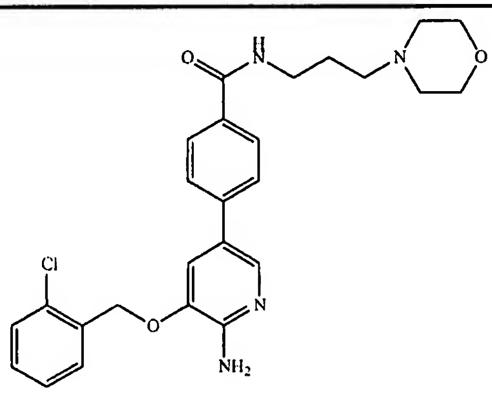
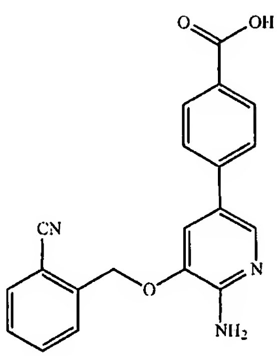
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-159		4-[6-Amino-5-(2-chloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	4.5	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.84(d, J=8.3 Hz, 2H), 7.55(d, J=8.3 Hz, 2H), 7.51(m, 2H), 7.43(m, 1H), 7.34(m, 2H), 7.24(d, J=1.8 Hz, 1H), 5.27(s, 2H), 4.97(br s, 2H), 3.75(m, 4H), 3.59(m, 2H), 3.25(m, 2H), 2.57(m, 4H), 1.83(m, 2H).	481
I-160		4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.35(s, 2H, CH_2), 5.95(br s, 2H, NH_2), 7.50-8.00(multiplets, 10H, aromatic	346

TABLE 2-continued

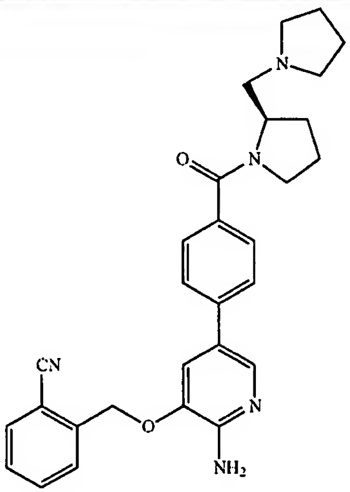
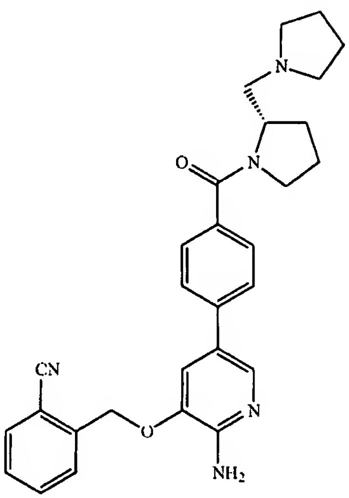
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-161		2-{2-Amino-5-[4-((2R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile	1.22	see examples	(300 MHz, $CDCl_3$) δ 7.99(d, J=1.6 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.50(m, 6H), 7.24(d, J=1.6 Hz, 1H), 5.35(s, 2H), 4.88(br s, 2H), 4.46(m, 1H), 3.52(m, 2H), 3.24(m, 4H), 2.2–1.5(m, 10H)	482
I-162		2-{2-Amino-5-[4-((2S)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile	2	see examples	^{1}H NMR(300 MHz, $CDCl_3$) δ 7.99(d, J=1.6 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.50(m, 6H), 7.24(d, J=1.6 Hz, 1H), 5.35 (s, 2H), 4.88(br s, 2H), 4.46(m, 1H), 3.52(m, 2H), 3.24(m, 4H), 2.2–1.5(m, 10H).	482

TABLE 2-continued

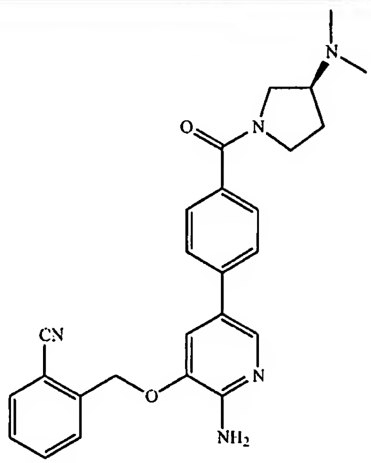
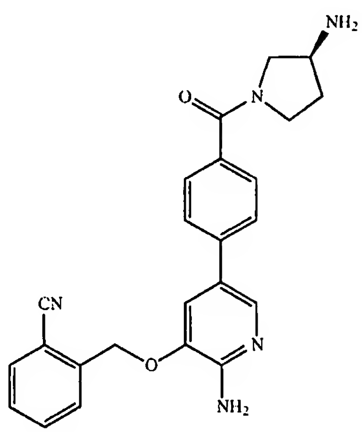
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-163		2-{2-Amino-5-[4-((3S)-3-dimethylamino-pyrrolidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile	>20	see examples	(300 MHz, $CDCl_3$) δ 7.98(s, 1H), 7.76(d, J=7.6 Hz, 2H), 7.50(m, 6H), 7.26(s, 1H), 5.38(s, 2H), 4.99(br s, 2H), 3.90(m, 1H), 3.60(m, 2H), 3.45(m, 1H), 2.85(m, 1H), 2.32(s, 3H), 2.23(s, 3H), 1.89(m, 2H)	442
I-164		2-{2-Amino-5-[4-((3S)-3-amino-pyrrolidine-1-carbonyl-phenyl]-pyridin-3-yloxymethyl}-benzonitrole	2.05	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.4 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.50(m, 6H), 7.24(d, J=1.4 Hz, 1H), 5.35(s, 2H), 4.91(br s, 2H), 3.70(m, 4H), 2.15(m, 1H), 2.23(s, 2H), 1.25(m, 1H), 1.05(m, 1H)	414

TABLE 2-continued

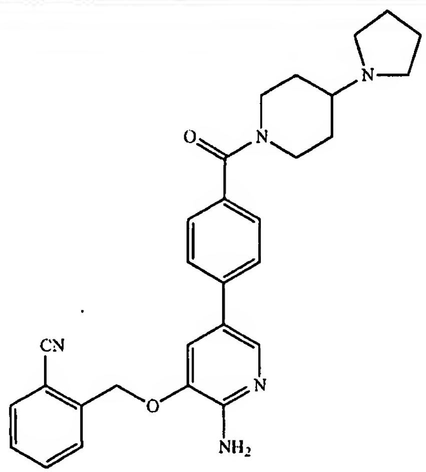
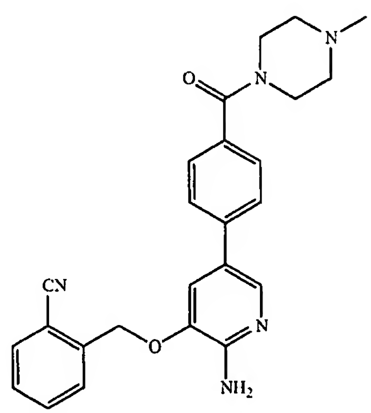
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-165		2-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile	3.9	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.66(m, 2H), 7.51(m, 2H), 7.46(m, 2H), 7.23(d, J=1.4 Hz, 1H), 5.35(s, 2H), 4.88(br s, 2H), 3.95(m, 4H), 2.55(m, 4H), 2.30 (m, 1H), 1.95(m, 2H), 1.76(m, 4H), 1.52(m, 2H)	482
I-166		2-{2-Amino-5-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzonitrile	3.2	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.8 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.66(m, 2H), 7.51(m, 2H), 7.48(m, 2H), 7.24(d, J=1.4 Hz, 1H), 5.35(s, 2H), 5.01(br s, 2H), 3.65(m, 4H), 2.45(m, 4H), 4H), 2.36(s, 3H)	428

TABLE 2-continued

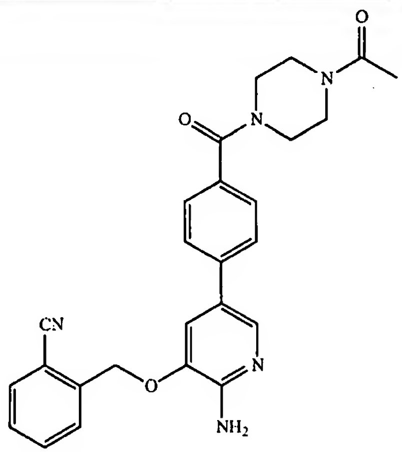
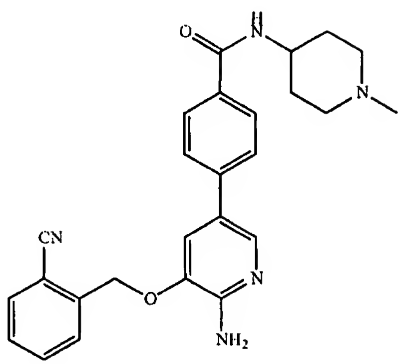
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-167		2-{5-[4-(4-Acetyl-piperazine-1-carbonyl)-phenyl]-2-amino-pyridin-3-yloxymethyl}-benzonitrile	5.7	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.7 Hz, 1H), 7.76(d, J=7.5 Hz, 2H), 7.66(m, 2H), 7.54(m, 2H), 7.50(m, 2H), 7.26(d, J=1.4 Hz, 1H), 5.36(s, 2H), 5.27(br s, 2H), 3.65(m, 8H), 2.14(s, 3H)	456
I-168		4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	10.8	see examples	(300 MHz, $CDCl_3$) δ 7.99(d, J=1.8 Hz, 1H), 7.82(d, J=8.3 Hz, 2H), 7.74(m, 1H), 7.66(m, 2H), 7.55(m, 3H), 7.25(d, J=1.8 Hz, 1H), 6.18(d, J=8.0 Hz, 1H), 5.35(s, 2H), 4.88(brs, 2H), 4.05(m, 1H), 2.96(m, 1H), 2.46(s, 3H), 2.40(m, 1H), 2.05(m, 1H), 1.79(m, 1H), 1.65(m, 2H), 0.95(m, 2H)	442

TABLE 2-continued

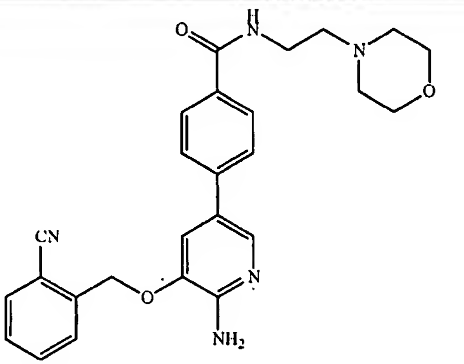
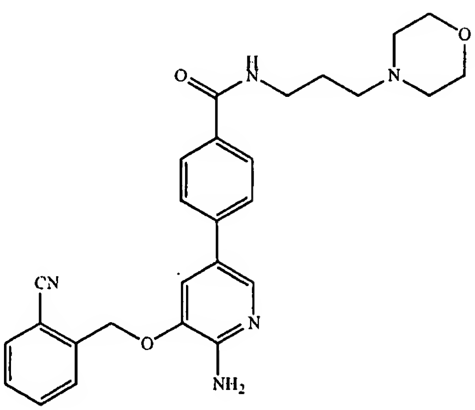
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-169		4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	8.6	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.85(d, J=8.4 Hz, 2H), 7.76(d, J=7.4 Hz, 1H), 7.66(m, 2H), 7.57(m, 3H), 7.27(d, J=1.8 Hz, 1H), 7.06(m, 1H), 5.36(s, 2H), 5.14(br s, 2H), 3.78(m, 4H), 3.63(m, 2H), 2.73(m, 2H), 2.63(m, 4H)	458
I-170		4-[6-Amino-5-(2-cyano-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	17.3	see examples	(300 MHz, $CDCl_3$) δ 8.01(d, J=1.7 Hz, 1H), 7.87(d, J=8.4 Hz, 2H), 7.76(d, J=7.5 Hz, 1H), 7.67(m, 1H), 7.56(d, J=8.4 Hz, 2H), 7.45(m, 3H), 7.27(d, J=1.8 Hz, 1H), 5.36 (s, 2H), 4.89(br s, 2H), 3.74(m, 4H), 3.60(m, 2H), 2.57(m, 6H), 1.82(m, 2H)	472

TABLE 2-continued

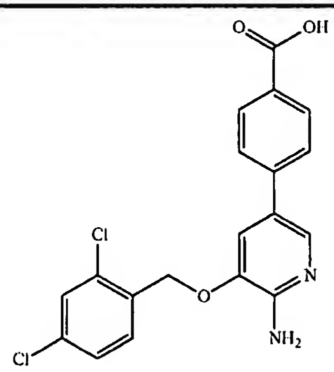
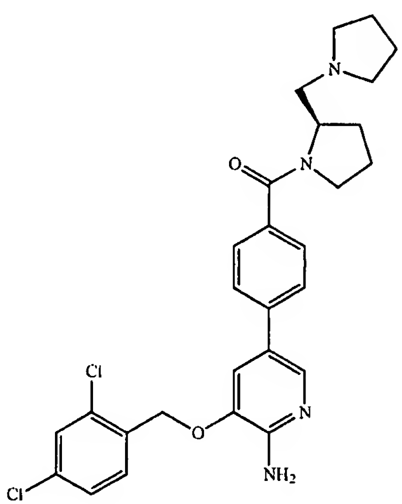
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-171		4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.35(s, 2H, CH_2), 5.90(br s, 2H, NH_2), 7.30-8.00(multiplets, 9H, aromatic)	389
I-172		{4-(6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.61	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.47(m, 6H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.18(d, J=1.7 Hz, 1H), 5.21(s, 2H), 4.85(br s, 2H), 4.42(m, 1H), 3.50(m, 2H), 2.84(m, 4H), 2.2-1.5(m, 10H)	527

TABLE 2-continued

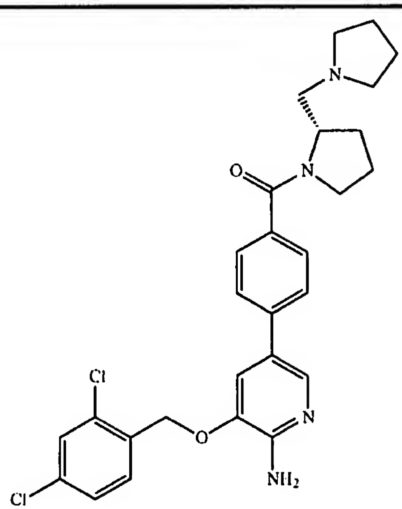
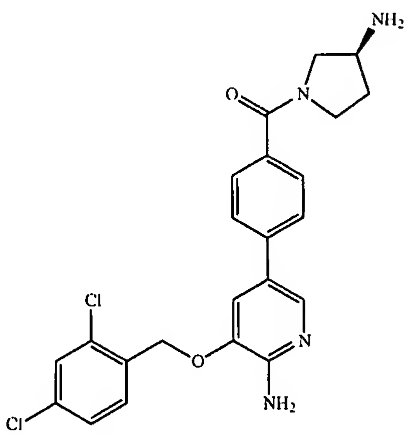
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-173		{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.66	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.47(m, 6H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.18(d, J=1.7 Hz, 1H), 5.21(s, 2H), 4.85(br s, 2H), 4.42(m, 1H), 3.50(m, 2H), 2.84(m, 4H), 2.2–1.5(m, 10H)	527
I-174		{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.8	see examples	(300 MHz, $CDCl_3$) δ 7.95(s, 1H), 7.50(m, 6H), 7.30(dd, J=1.9 Hz, J=8.3 Hz, 1H), 7.20(s, 1H), 5.21(s, 2H), 5.07 (br s, 2H), 3.90(m, 1H), 3.62(m, 2H), 3.45(m, 1H), 2.85(m, 1H), 2.32(s, 3H), 2.23(s, 3H), 1.89(m, 2H)	486

TABLE 2-continued

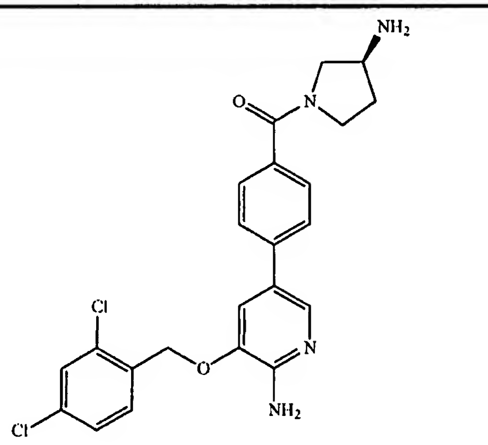
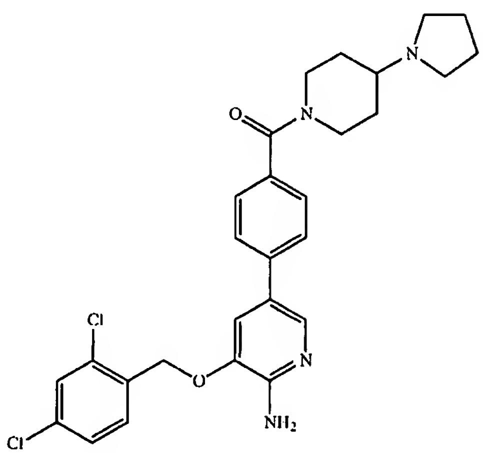
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-175		{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	1.2	see examples		458
I-176		{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.85	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.8 Hz, 1H), 7.71(d, J=3.5 Hz, 1H), 7.50(m, 5H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.18(d, J=1.8 Hz, 1H), 5.22(s, 2H), 4.83(br s, 2H), 4.23(m, 2H), 2.78(m, 2H), 1.95(m, 2H), 1.76(m, 3H), 1.25 (m, 4H), 0.85(m, 4H)	525

TABLE 2-continued

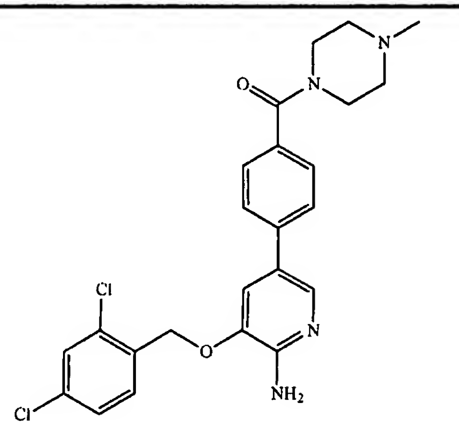
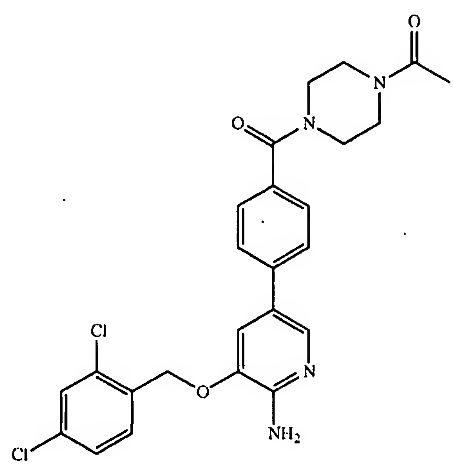
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-177		{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.79	see examples	(300 MHz, $CDCl_3$) δ 7.95(s, 1H), 7.50(m, 6H), 7.30(dd, J=1.9 Hz, J=8.3 Hz, 1H), 7.20(s, 1H), 5.21(s, 2H), 5.07(br s, 2H), 3.65(m, 4H), 2.45(m, 4H), 2.36(s, 3H)	473
I-178		1-(4-{4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	1.67	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.8 Hz, 1H), 7.50(m, 6H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.18(d, J=1.8 Hz, 1H), 5.22(s, 2H), 4.87(br s, 2H), 3.64(m, 4H), 3.53(m, 4H), 2.14(s, 3H)	501

TABLE 2-continued

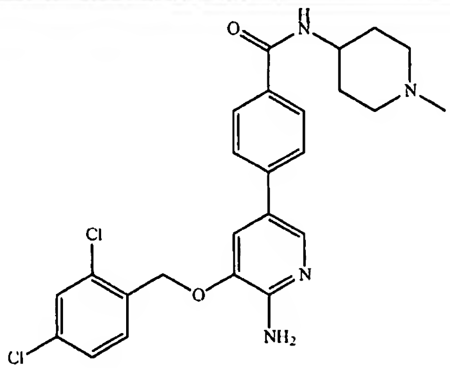
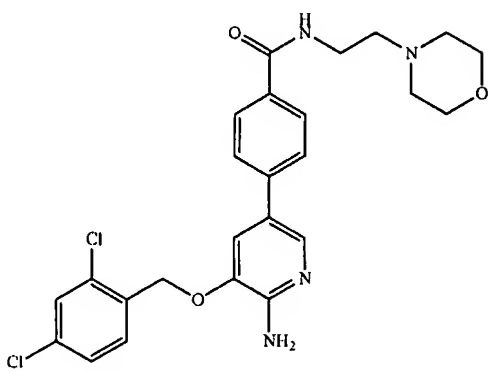
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-179		4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	1.12	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.81(d, J=8.3 Hz, 2H), 7.55(d, J=8.3 Hz, 2H), 7.46(m, 2H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.18(d, J=1.8 Hz, 1H), 6.09(br d, 1H), 5.22(s, 2H), 4.83 (br s, 2H), 4.05(m, 1H), 3.06 (m, 1H), 2.46(s, 3H), 2.32(m, 1H), 2.12(m, 1H), 1.83(m, 1H), 1.26(m, 2H), 0.88(m, 2H)	486
I-180		4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	3.8	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.84(d, J=8.3 Hz, 2H), 7.56(d, J=8.3 Hz, 2H), 7.46(m, 2H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.20(d, J=1.8 Hz, 1H), 6.90(br t, 1H), 5.22 (s, 2H), 4.91(br s, 2H), 3.75(m, 4H), 3.59(m, 2H), 2.65(m, 2H), 2.55(m, 4H)	502

TABLE 2-continued

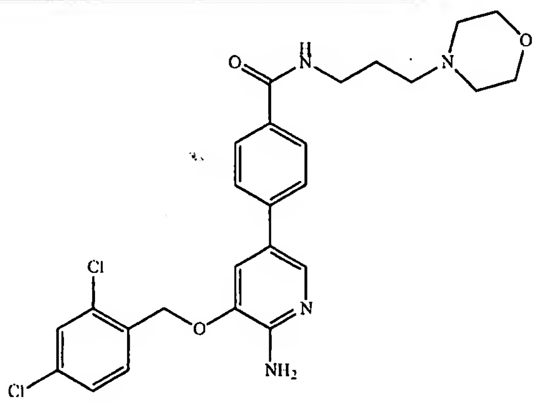
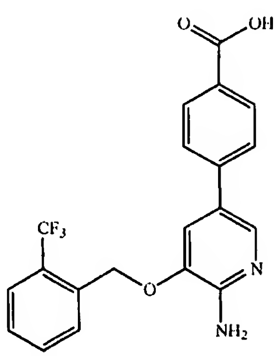
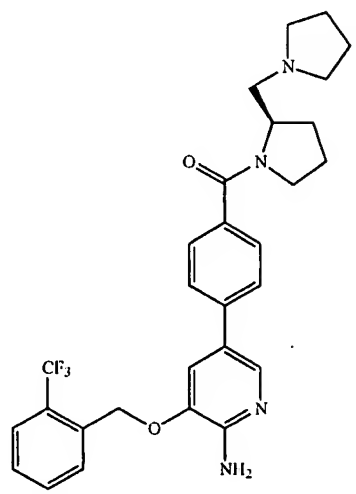
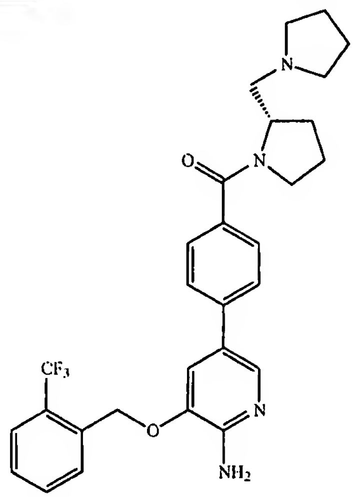
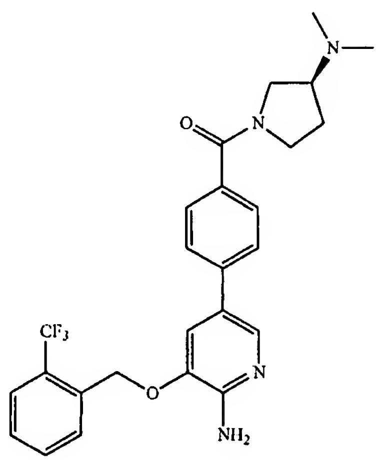
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
I-181		4-[6-Amino-5-(2,4-dichloro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	2	see examples	(300 MHz, $CDCl_3$) δ 7.99(d, J=1.7 Hz, 1H), 7.87(d, J=8.3 Hz, 2H), 7.71(m, 1H), 7.55(d, J=8.3 Hz, 2H), 7.47(m, 2H), 7.30(dd, J=2.0 Hz, J=8.3 Hz, 1H), 7.21 (d, J=1.7 Hz, 1H), 5.23(s, 2H), 4.91(br s, 2H), 3.75(m, 4H), 3.59(m, 2H), 2.60(m, 6H), 1.83(m, 2H)	516
I-182		4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.35(s, 2H, CH_2), 5.95(br s, 2H, NH_2), 7.40–8.00 (multiplets, 10H, aromatic)	388 (M+)

TABLE 2-continued

No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
I-183		{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.75	see examples	^{1}H NMR(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.74(d, J=7.8 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.53(m, 6H), 7.15(d, J=1.7 Hz, 1H), 5.35(s, 2H), 4.82(br s, 2H), 4.42(m, 1H), 3.50(m, 2H), 2.65 (m, 4H), 2.2–1.5(m, 10H)	525

I-184		{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	>20	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.74(d, J=7.8 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.53(m, 6H), 7.15(d, J=1.7 Hz, 1H), 5.35(s, 2H), 4.82(br s, 2H), 4.42(m, 1H), 3.50(m, 2H), 2.65 (m, 4H), 2.2–1.5(m, 10H)	525
I-185		{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	1.39	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=2.1 Hz, 1H), 7.74(d, J=7.8 Hz, 1H), 7.88(d, J=7.7 Hz, 1H), 7.51(m, 6H), 7.16(d, J=2.1 Hz, 1H), 5.35(s, 2H), 4.88(br s, 2H), 3.89(m, 1H), 3.65(m, 2H), 3.45 (m, 1H), 2.75(m, 1H), 2.31(s, 3H), 2.22(s, 3H), 2.11(m, 1H), 1.89(m, 1H).	485

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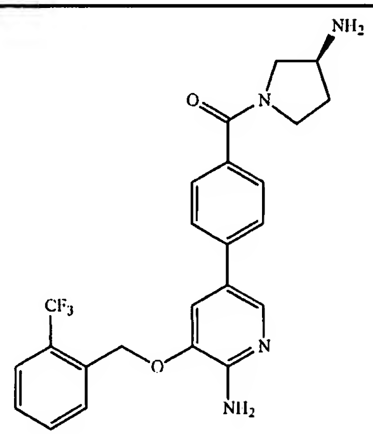
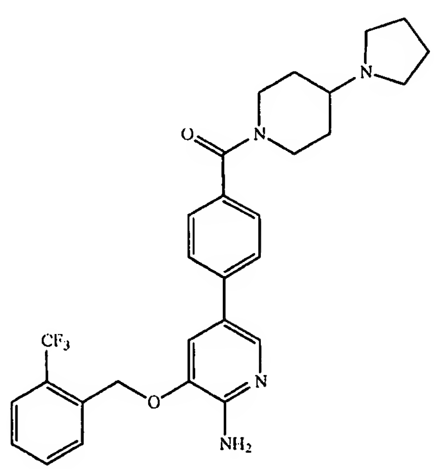
I-186		[(3S)-3-Amino-pyrrolidin-1-yl]-{4-[6-amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-methanone	0.79	see examples	(300 MHz, $CDCl_3$) δ 7.93(d, J=1.4 Hz, 1H), 7.74(d, J=7.7 Hz, 1H), 7.67(d, J=7.4 Hz, 1H), 7.55(m, 3H), 7.45(m, 3H), 7.15(d, J=1.4 Hz, 1H), 5.35(s, 2H), 5.01(br s, 2H), 3.65(m, 4H), 2.03 (m, 3H), 1.75(m, 1H), 0.85(m, 1H)	457
I-187		{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	1.01	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.8 Hz, 1H), 7.74(d, J=7.9 Hz, 1H), 7.66(m, 1H), 7.60(m, 1H), 7.47(m, 5H), 7.14(d, J=1.8 Hz, 1H), 5.35(s, 2H), 4.81(br s, 2H), 4.60(m, 1H), 3.74(m, 1H), 2.96(m, 2H), 2.65(m, 2H), 2.22(m, 1H), 1.85(m, 2H), 1.55(m, 4H), 1.25(m, 2H), 0.95(m, 2H)	525

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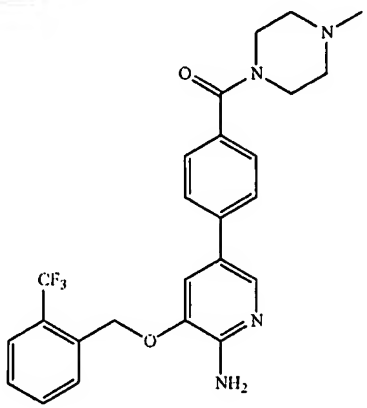
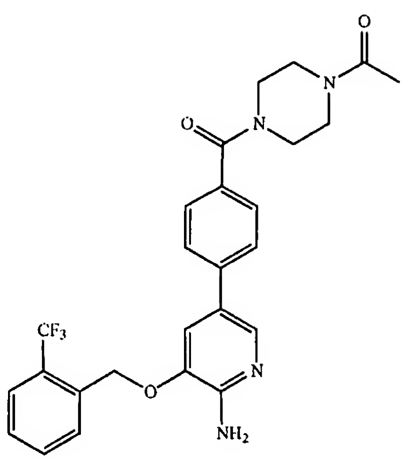
I-188		{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	1.64	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.74(d, J=7.7 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.60(t, J=7.7 Hz, 1H), 7.48(m, 5H), 7.14(d, J=1.8 Hz, 1H), 5.35 (s, 2H), 4.89(br s, 2H), 3.80 (m, 2H), 3.51(m, 2H), 2.40 (m, 4H), 2.32(s, 3H)	471
I-189		1-(4-{4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	6.7	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.8 Hz, 1H), 7.74(d, J=7.7 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.60(t, J=7.7 Hz, 1H), 7.48(m, 5H), 7.14(d, J=1.8 Hz, 1H), 5.36 (s, 2H), 4.87(br s, 2H), 3.64 (m, 4H), 3.53(m, 4H), 2.14 (s, 3H)	499

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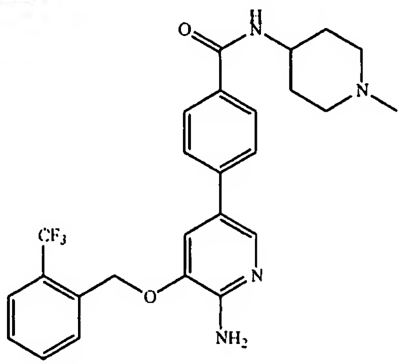
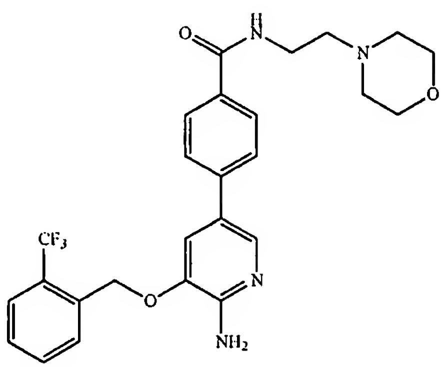
I-190		4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	3.8	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.79(d, J=8.3 Hz, 2H), 7.74(d, J=7.8 Hz, 1H), 7.67(d, J=7.6 Hz, 1H), 7.60(m, 1H), 7.52(m, 3H), 7.14(d, J=1.8 Hz, 1H), 5.98(m, 1H), 5.36 (s, 2H), 4.85(br s, 2H),), 4.05(m, 1H), 2.90(m, 2H), 2.32 (s, 3H), 2.18 (m, 2H), 2.01(m, 2H), 1.62(m, 2H)	485
I-191		4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	5.2	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.82(d, J=8.4 Hz, 2H), 7.74(d, J=7.8 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.60(t, , J=7.7 Hz, 1H), 7.53(m, 3H), 7.17(d, J=1.8 Hz, 1H), 6.83(m, 1H), 5.36(s, 2H), 4.89 (br s, 2H), 3.74(m, 4H), 3.57(m, 2H), 2.62(m, 2H), 2.52(m, 4H)	501

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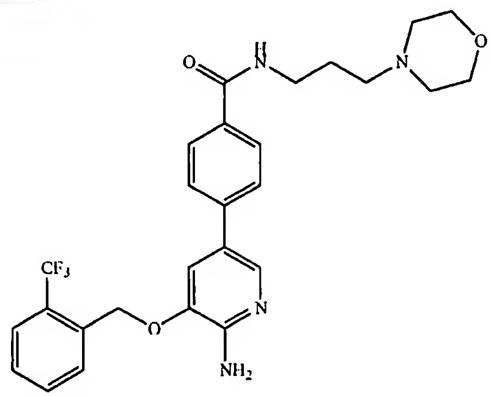
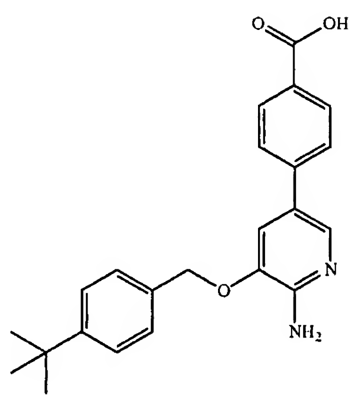
I-192		4-[6-Amino-5-(2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	3.8	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.8 Hz, 1H), 7.95(m, 1H), 7.86(d, J=8.4 Hz, 2H), 7.74(d, J=7.7 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.60(t, J=7.7 Hz, 1H), 7.53(m, 3H), 7.17(d, J=1.8 Hz, 1H), 5.36(s, 2H), 4.94(br s, 2H), 4.94(brs, 2H), 3.75(m, 4H), 3.59(m, 2H), 2.59(m, 6H), 1.83(m, 2H)	515
I-193		4-{6-Amino-5-(4-#tert-butyl-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 1.25(s, 9H, t-butyl), 5.20(s, 2H, CH_2), 5.95(br s, 2H, NH_2), 7.35-8.00 (multiplets, 10H, aromatic)	376 (M+)

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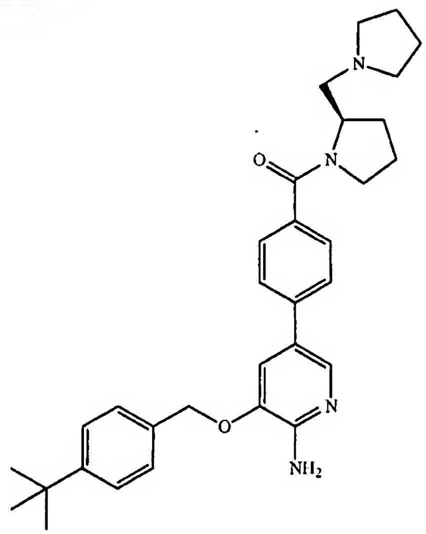
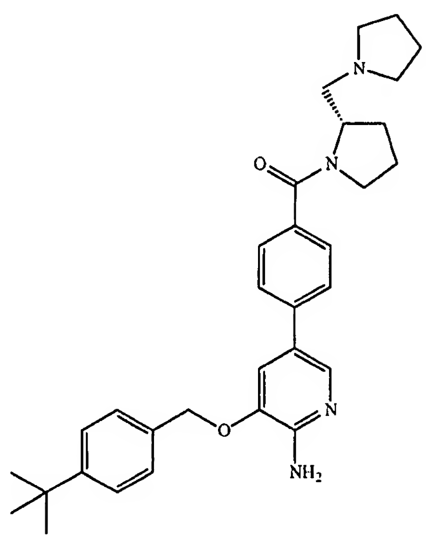
I-194		{4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.89	see examples	(300 MHz, $CDCl_3$) δ 7.94(d, J=1.7 Hz, 1H), 7.49(m, 8H), 7.21(d, J=1.7 Hz, 1H), 5.11(s, 2H), 4.80(br s, 2H), 4.48(m, 1H), 3.48(m, 2H), 2.62(m, 4H), 2.2–1.5(m, 10H), 1.34(s, 9H)	513
I-195		{4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	3.27	see examples	(300 MHz, $CDCl_3$) δ 7.94(d, J=1.7 Hz, 1H), 7.49(m, 8H), 7.21(d, J=1.7 Hz, 1H), 5.11(s, 2H), 4.80(br s, 2H), 4.48(m, 1H), 3.48(m, 2H), 2.62(m, 4H), 2.2–1.5(m, 10H), 1.34(s, 9H)	513

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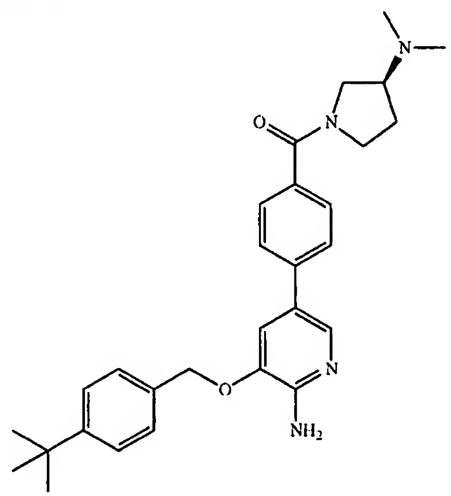
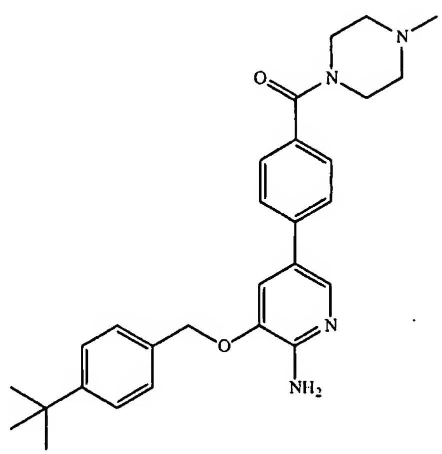
I-196		{4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone	4.29	see examples	(300 MHz, $CDCl_3$) δ 7.94(d, J=2.1 Hz, 1H), 7.54(m, 4H), 7.45(d, J=8.3 Hz, 2H), 7.38(d, J=8.3 Hz, 2H), 7.21(d, J=1.7 Hz, 1H), 5.11(s, 2H), 4.84(br s, 2H), 3.89(m, 1H), 3.64 (m, 2H), 3.42(m, 1H), 2.70(m, 1H), 2.31(s, 3H), 2.22(s, 3H), 2.05(m, 1H), 1.89(m, 1H), 1.34(s, 9H)	473
I-197		{4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	3.8	see examples	(300 MHz, $CDCl_3$) δ 7.93(d, J=1.7 Hz, 1H), 7.48(m, 4H), 7.41(m, 4H), 7.21(d, J=1.7 Hz, 1H), 5.11(s, 2H), 4.85(br s, 2H), 3.80(m, 2H), 3.52(m, 2H), 2.41(m, 4H), 2.33(s, 3H), 1.34(s, 9H)	459

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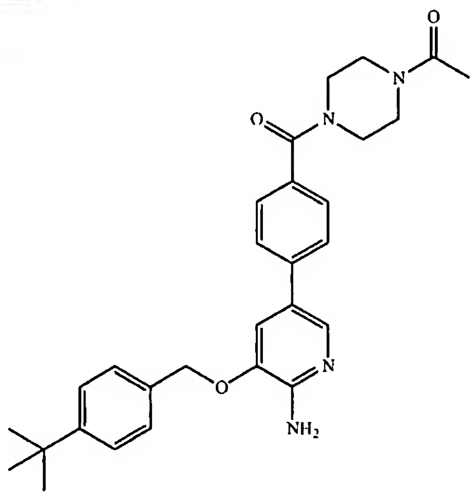
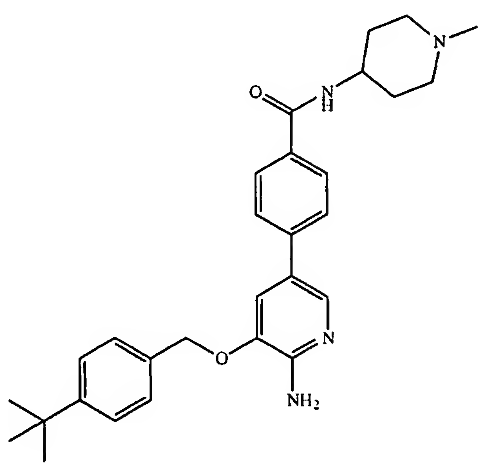
I-198		1-(4-{4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	3	see examples	(300 MHz, $CDCl_3$) δ 7.94(d, J=1.8 Hz, 1H), 7.50(m, 8H), 7.21(d, J=1.7 Hz, 1H), 5.11(s, 2H), 4.90(br s, 2H), 3.64(m, 4H), 3.53(m, 4H), 2.14(s, 3H), 1.34(s, 9H)	487
I-199		4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	2.92	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.80(d, J=8.3 Hz, 2H), 7.54(d, J=8.3 Hz, 2H), 7.44(d, J=7.7 Hz, 2H), 7.38(d, J=7.7 Hz, 2H), 7.21(d, J=1.8 Hz, 1H), 6.05(m, 1H), 5.11(s, 2H), 4.80(br s, 2H), 4.01(m, 1H), 2.84(m, 2H), 2.33(s, 3H), 2.20(m, 2H), 2.10(m, 2H), 1.62(m, 2H), 1.34(s, 9H)	487

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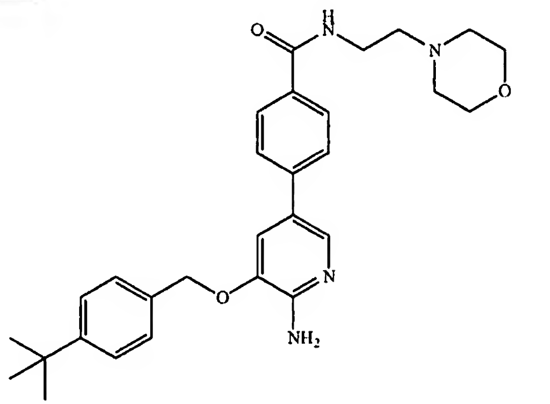
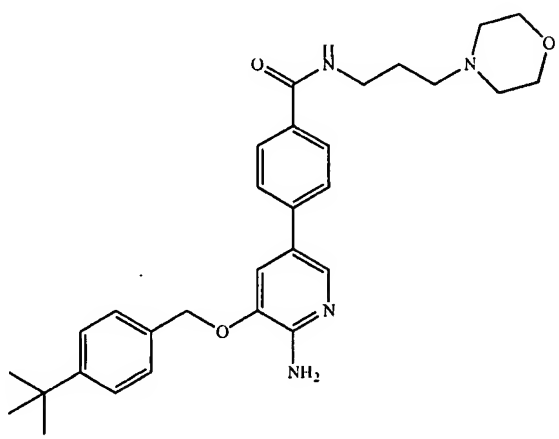
I-200		4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	6.88	see examples	(300 MHz, $CDCl_3$) δ 7.95(d, J=1.8 Hz, 1H), 7.82(d, J=8.3 Hz, 2H), 7.54(d, J=8.3 Hz, 2H), 7.44(d, J=8.4 Hz, 2H), 7.38(d, J=8.4 Hz, 2H), 7.22(d, J=1.8 Hz, 1H), 6.91(t, J=4.6 Hz, 1H), 5.10(s, 2H), 4.90(br s, 2H), 3.74(m, 4H), 3.57 (m, 2H), 2.62(m, 2H), 2.51(m, 4H), 1.34(s, 9H)	489
I-201		4-[6-Amino-5-(4-tert-butyl-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	6.3	see examples	(300 MHz, $CDCl_3$) δ 8.01(t, J=4.5 Hz, 1H), 7.96(d, J=1.8 Hz, 1H), 7.86(d, J=8.3 Hz, 2H), 7.54(d, J=8.3 Hz, 2H), 7.44(d, J=8.4 Hz, 2H), 7.38(d, J=8.4 Hz, 2H), 7.24(d, J=1.8 Hz, 1H), 5.12 (s, 2H), 4.89(br s, 2H), 3.74(m, 4H), 3.59 (m, 2H), 2.55(m, 6H), 1.82(m, 2H), 1.34(s, 9H)	503

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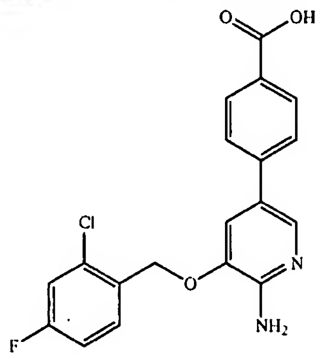
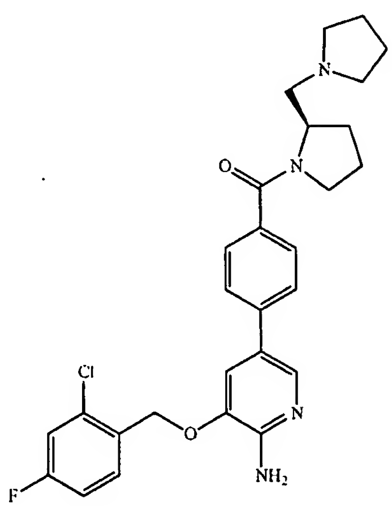
I-202		4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoic acid		see examples	(400 MHz, DMSO-d_6) δ 5.25(s, 2H, CH_2), 5.80(br s, 2H, NH_2), 7.20–8.00(multiplets, 9H, aromatic)	374
I-203		{4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	1.48	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.05(m, 1H), 5.21(s, 2H), 4.80(br s, 2H), 4.45(m, 1H), 3.52(m, 2H), 2.76(m, 4H), 2.2–1.5 (m, 10H)	509

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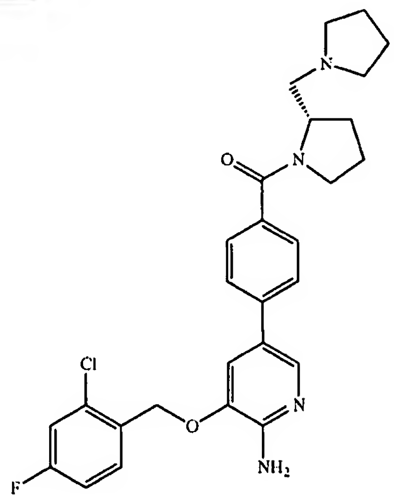
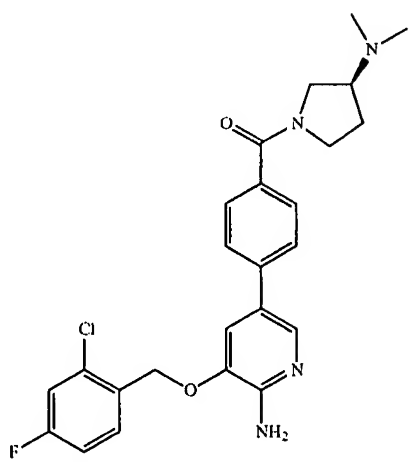
I-204		{4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	2.5	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.05(m, 1H), 5.21(s, 2H), 4.80(br s, 2H), 4.45(m, 1H), 3.52(m, 2H), 2.76(m, 4H), 2.2–1.5 (m, 10H)	509
I-205		{4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	61	see examples	(300 MHz, $CDCl_3$) δ 7.97(s, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.04(m, 1H), 5.21(s, 2H), 4.95(br s, 2H), 3.90(m, 1H), 3.61(m, 2H), 3.33(m, 1H), 2.75(m, 1H), 2.32(s, 3H), 2.23(s, 3H), 2.10(m, 1H), 1.89 (m, 1H)	469

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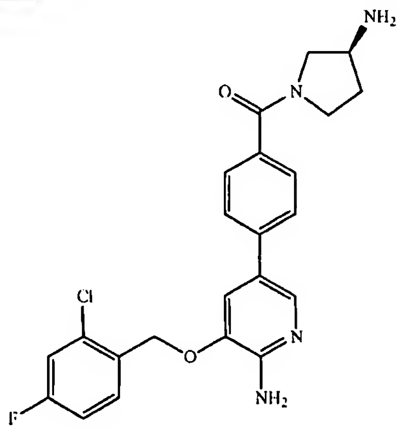
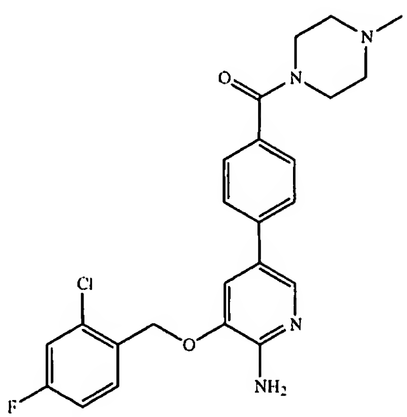
I-206		{4-(6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	1.83	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.8 Hz, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.04(m, 1H), 5.21(s, 2H), 4.84(brs, 2H), 3.84(m, 4H), 2.15(m, 1H), 1.76(m, 2H), 1.56(m, 2H)	441
I-207		{4-(6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	5	see examples	(300 MHz, $CDCl_3$) δ 7.96(s, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.04(m, 1H), 5.21(s, 2H), 4.89(br s, 2H), 3.80(m, 2H), 3.65 (m, 2H), 2.43(m, 4H), 2.33(s, 3H)	456

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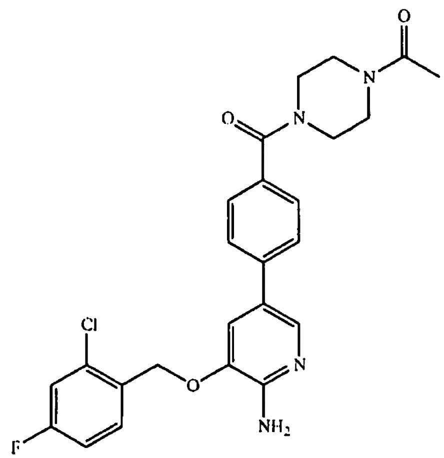
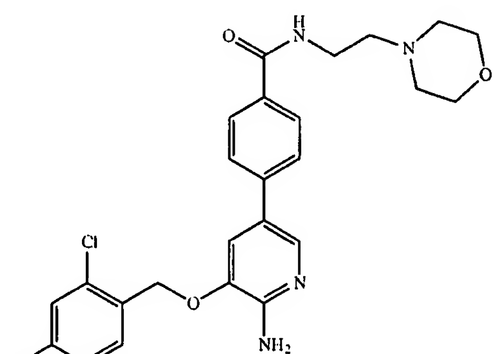
I-208		1-(4-{4-(6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-benzoyl}-piperazin-1-yl)-ethanone	5.3	see examples	(300 MHz, $CDCl_3$) δ 7.96(s, 1H), 7.52(m, 6H), 7.20(m, 1H), 7.04(m, 1H), 5.21(s, 2H), 4.90(br s, 2H), 3.67(m, 4H), 3.53 (m, 4H), 2.22(s, 3H)	483
I-209		4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	11	see examples	(300 MHz, $CDCl_3$) δ 7.99(d, J=1.6 Hz, 1H), 7.84(d, J=8.3 Hz, 2H), 7.57(d, J=8.3 Hz, 2H), 7.49(dd, J=6.0 Hz, 8.5 Hz, 1H), 7.20(m, 2H), 7.04(m, 1H), 6.82(m, 1H), 5.22(s, 2H), 4.85(br s, 2H), 3.74(m, 4H), 3.58(m, 2H), 2.63 (m, 2H), 2.53(m, 4H)	485

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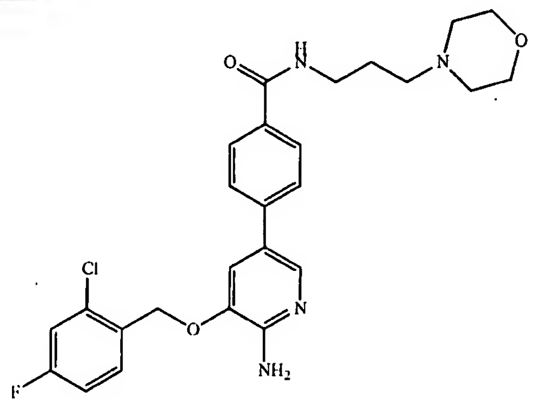
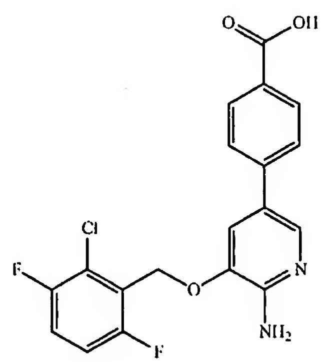
I-210		4-[6-Amino-5-(2-chloro-4-fluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	5.8	see examples	(300 MHz, $CDCl_3$) δ 8.06(m, 1H), 7.00(d, J=1.6 Hz, 1H), 7.89(d, J=8.3 Hz, 2H), 7.55(d, J=8.3 Hz, 2H), 7.49(dd, J=6.0 Hz, 8.5 Hz, 1H), 7.20(m, 2H), 7.04(m, 1H), 5.22(s, 2H), 4.85(br s, 2H), 3.75(m, 4H), 3.60(m, 2H), 2.55 (m, 6H), 1.83(m, 2H)	499
I-211		4 [6 Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid	0.35	see examples	(300 MHz, DMSO-d_6) δ 5.21(s, 2H), 5.71(s, 2H), 7.31–7.46(m, 1H), 7.5–7.62 (m, 4H), 7.91–7.94(m, 3H).	

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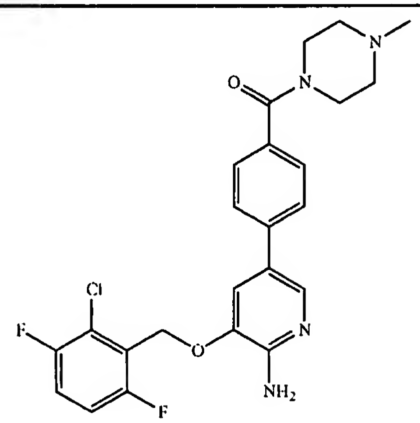
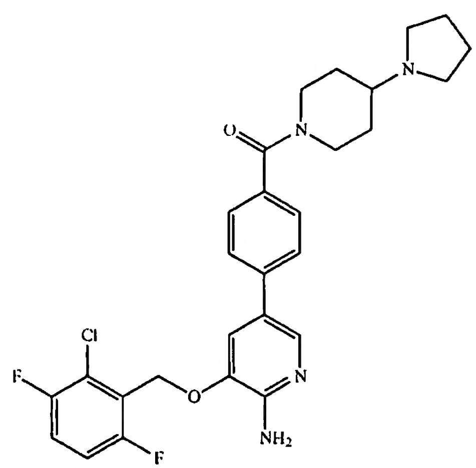
I-212		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.063	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.6 Hz, 1H), 7.56(d, J=8.2 Hz, 2H), 7.48(d, J=8.2 Hz, 2H), 7.35(d, J=1.6 Hz, 1H), 7.20 (m, 1H), 7.06(m, 1H). 5.29(s, 2H), 4.81 (br s, 2H), 3.79(m, 2H), 3.54(m, 2H), 2.44(m, 4H), 2.33(s, 3H)	473
I-213		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.049	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.7 Hz, 1H), 7.55(d, J=8.2 Hz, 2H), 7.45(d, J=8.2 Hz, 2H), 7.35(d, J=1.6 Hz, 1H), 7.20(m, 1H), 7.06(m, 1H), 5.29 (5. 2H), 4.79(br s, 2H), 4.60(m, 1H), 3.85(m, 1H), 3.02(m, 2H), 2.65(m, 4H), 2.35 (m, 1H), 2.05(m, 4H), 1.65(m, 4H).	527

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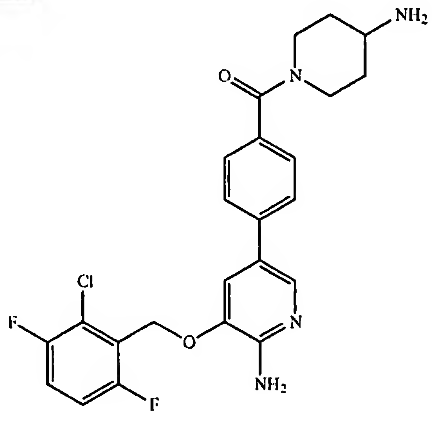
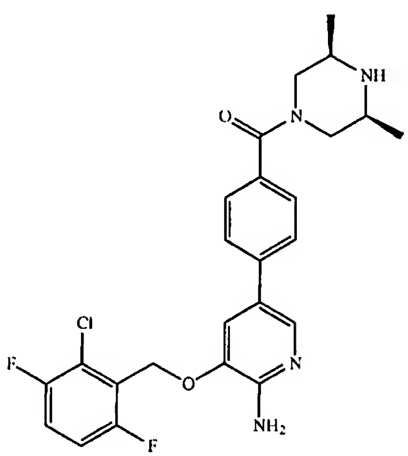
I-214		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-amino-piperidin-1-yl)-methanone	0.1	see examples	(400 MHz, DMSO-d_6) δ 7.92(s, 1H), 7.66(m, 4H), 7.46(m, 4H), 5.89(s, 2H), 5.39(s, 2H), 4.19(m, 1H), 3.50(m, 2H), 2.54(m, 5H), 1.95(m, 2H), 1.83(m, 3H), 1.64(m, 4H)	MS (ES+) m/z 543 (MH+) MS m/z 473 [M + 1]
I-215		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	0.1	see examples	(400 MHz, DMSO-d_6) δ 7.98(s, 1H), 7.58 (d, 2H), 7.41(d, 2H), 7.31(s, 1H), 7.19(m, 1H), 7.06(m, 1H), 5.31(s, 2H), 4.81(m, 2H), 4.68(m, 1H), 3.69(m, 1H), 2.89(m, 2H), 2.69(m, 1H), 2.40(m, 1H), 1.74(m, 1H), 1.18 (d, 6H)	487

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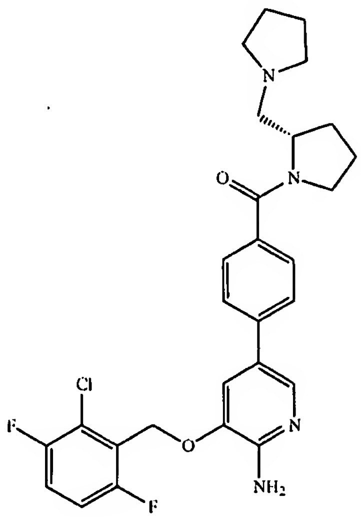
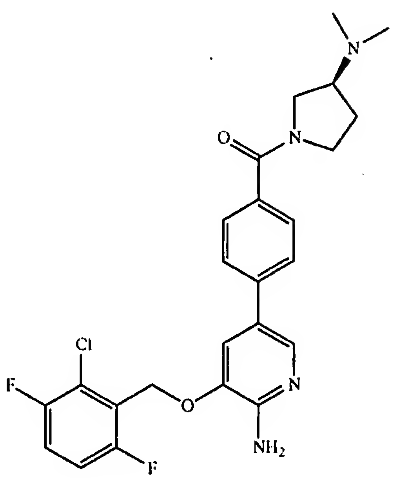
I-216		{4-[6-Amino-5-(2-chlora-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.1	see examples	(400 MHz, DMSO-d_6) δ 7.95(d, 1H), 7.69(d, 2H), 7.58(m, 2H), 7.50(d, 2H), 7.40(m, 1H), 5.81(s, 2H), 5.29(s, 2H), 4.35(m, 1H), 3.5(d, 2H), 2.87(d, 2H), 2.71(d, 2H), 1.7–2.0 (m, 10H)	527
I-217		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.12	see examples	(400 MHz, DMSO-d_6) δ 7.97(s, 1H), 7.60(m, 4H), 7.32(s, 1H), 7.18(m, 1H), 7.04(m, 1H), 5.31(s, 2H), 4.78(m, 2H), 3.90(m, 1H), 3.68(m, 2H), 3.41(m, 1H), 2.78(m, 1H), 2.31(s, 3H), 2.24(s, 3H), 2.08(m, 1H), 1.84(m, 1H)	487

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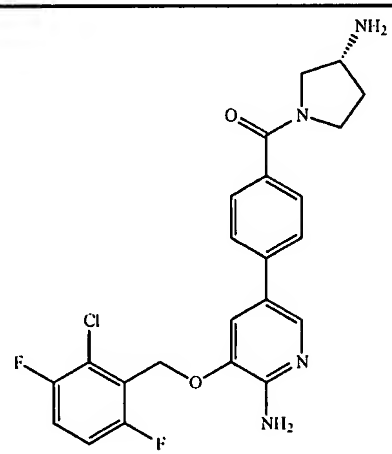
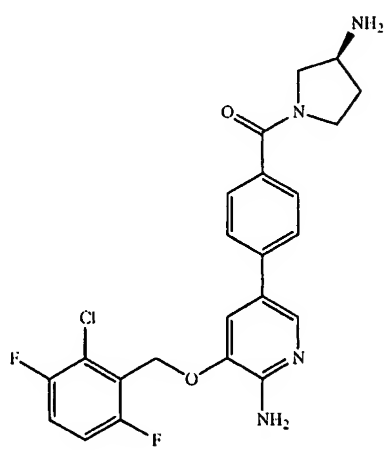
I-218		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone	0.053	see examples	(400 MHz, DMSO-d_6) δ 7.84(s, 1H), 7.62(m, 5H), 7.35(m, 1H), 7.20(m, 1H), 5.38(s, 2H), 3.78(m, 3H), 3.55(m, 1H), 3.41(m, 1H), 2.18(m, 1H), 1.82(m, 1H)	459
I-219		{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	0.095	see examples	400 MHz, DMSO-d_6) δ 7.84(s, 1H), 7.62(m, 5H), 7.35(m, 1H), 7.20(m, 1H), 5.38(s, 2H), 3.78(m, 3H), 3.55(m, 1H), 3.41(m, 1H), 2.18(m, 1H), 1.82(m, 1H)	459

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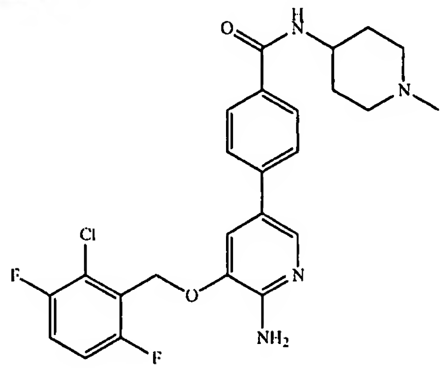
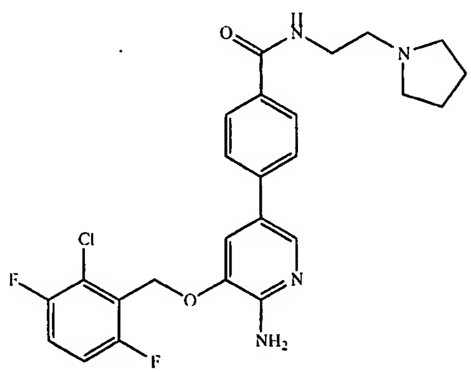
I-220		4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	0.11	see examples	(400 MHz, DMSO-d_6) δ 7.97(s, 1H), 7.80(d, 2H), 7.58(d, 2H), 7.36(s, 1H), 7.18(m, 1H), 7.04(m, 1H), 6.01(d, 1H), 5.28(s, 2H), 4.78(s, 2H), 3.98(m, 1H), 2.85(m, 2H), 2.31(s, 3H), 2.18(t, 2H), 2.10(m, 2H), 1.65(m, 2H)	487
I-221		4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-pyrrolidin-1-yl)-ethyl)-benzamide	0.18	see examples	(400 MHz, DMSO-d_6) δ 7.98(s, 1H), 7.89(d, 2H), 7.56(d, 2H), 7.45(m, 1H), 7.31(s, 1H), 7.17(m, 1H), 7.01(m, 1H), 5.28(s, 2H), 4.85(s, 2H), 3.65(m, 2H), 2.89(t, 2H), 2.76(m, 4H), 1.89(m, 4H)	487

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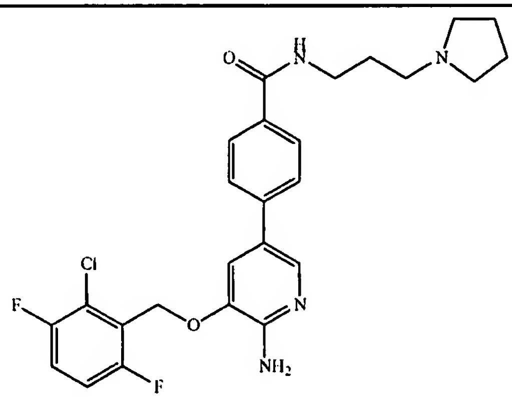
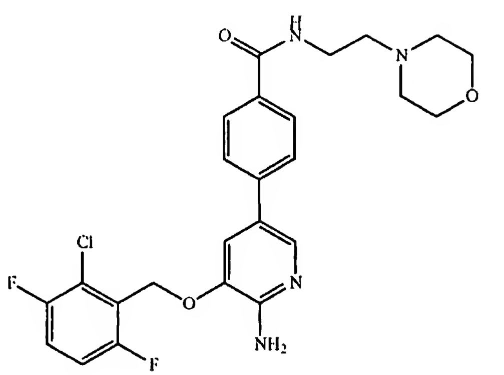
I-222		4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-pyrrolidin-1-yl)-propyl)-benzamide	0.19	see examples	(400 MHz, DMSO-d_6) δ 8.72(m, 1H), 7.95(m, 3H), 7.57(d, 2H), 7.35(s, 1H), 7.18(m, 1H), 7.02(m, 1H), 5.31(s, 2H), 4.79(s, 2H), 3.68(m, 2H), 2.89(m, 6H), 1.97(m, 6H)	501
I-223		4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl)-ethyl)-benzamide	0.165	see examples	(400 MHz, DMSO-d_6) δ 7.97(s, 1H), 7.82(d, 2H), 7.62(d, 2H), 7.36(s, 1H), 7.18(m, 1H), 7.05(m, 1H), 6.81(m, 1H), 5.28(s, 2H), 4.79(s, 2H), 3.78(m, 4H), 3.58(m, 2H), 2.83(t, 2H), 2.51(m, 4H)	503

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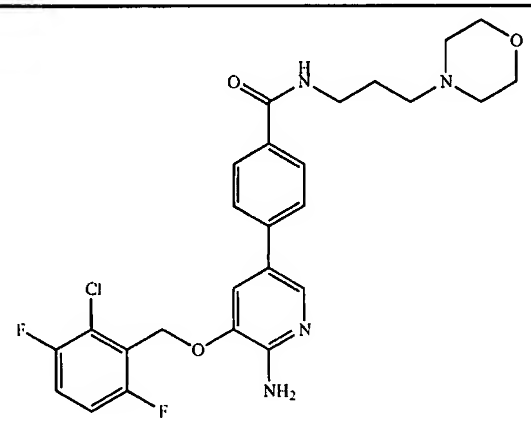
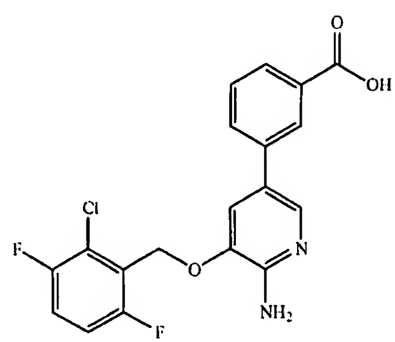
I-224		4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	0.28	see examples	(400 MHz, DMSO-d_6) δ 8.04(m, 1H), 7.96(s, 1H), 7.89(d, 2H), 7.58(d, 2H), 7.38(s, 1H), 7.18(m, 1H), 7.06(m, 1H), 7.29(s, 2H), 4.81(s, 2H), 3.76(m, 4H), 3.61(m, 2H), 2.59(t, 2H), 2.54(m, 4H), 1.79(m, 2H)	517
I-225		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzoic acid	3.7/0.6	see examples	(300 MHz, $CDCl_3$) δ 8.15(s, 1H), 7.92 (s, 1H), 7.84(d, J=7.4 Hz, 1H), 7.60(m, 2H), 7.55(s, 1H), 7.40(m, 2H), 5.75(s, 2H), 5.31(br s, 2H)	391

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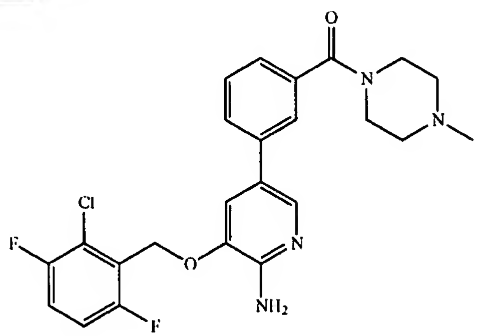
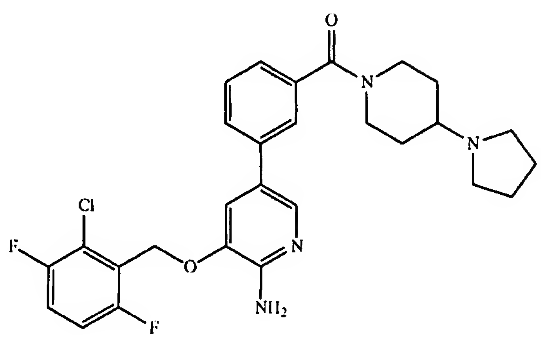
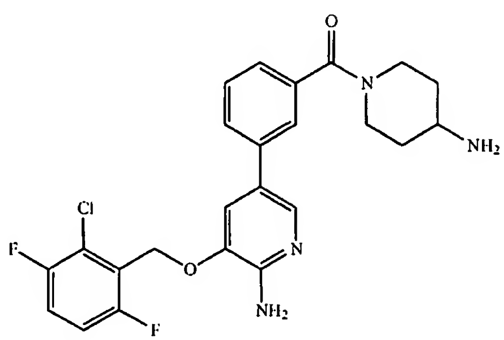
I-226		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.068	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.58(dd, J=1.1 Hz, 6.8 Hz, 1H), 7.46 (m, 1H), 7.35(m, 3H), 7.20(m, 1H), 7.06 (m, 1H), 5.27(s, 2H), 4.81(br s, 2H), 3.83(m, 2H), 3.50(m, 2H), 2.49 (m, 2H), 2.39(m, 2H), 3.33(s, 3H)	473
I-227		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.05	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.8 Hz, 1H), 7.57(dd, J=1.2 Hz, 8.0 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.34(m, 3H), 7.20(m, 1H), 7.06(m, 1H), 5.27(s, 2H), 4.77(br s, 2H), 4.60(m, 1H), 3.80(m, 1H), 3.02(m, 2H), 2.60(m, 2H), 2.30 (m, 1H), 1.95(m, 2H), 1.85(m, 4H), 1.65(m, 4H)	527
I-228		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-amino-piperidin-1-yl)-methanone	0.23	see examples	(300 MHz, CD_3OD) δ 8.01(s, 1H), 7.89 (s, 1H), 7.75(m, 2H), 7.59(s, 1H), 7.48(t, 1H), 7.31(m, 1H), 7.18(m, 1H), 5.38(s, 2H), 4.01(m, 1H), 3.09(m, 2H), 2.68(t, 2H), 1.97(m, 2H), 1.58(m, 2H)	473

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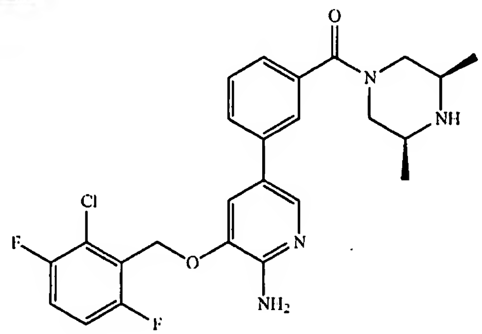
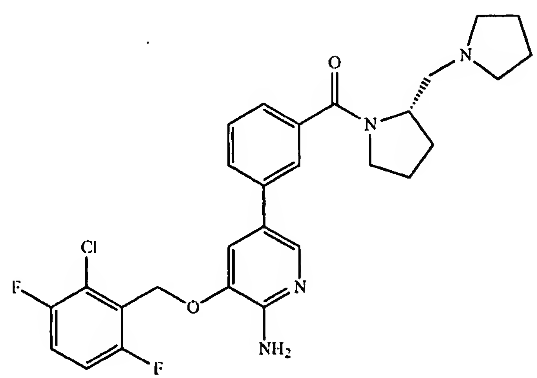
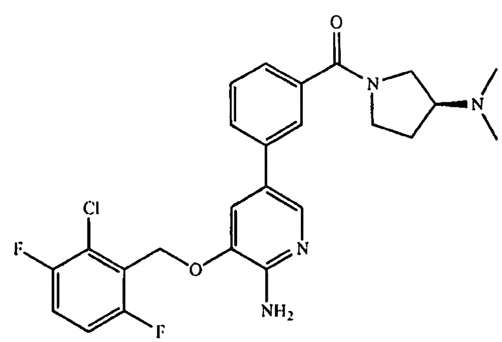
I-229		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	0.066/ 0.18	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.56(m, 1H), 7.47(t, J=7.6 Hz, 1H), 7.36(m, 3H), 7.20(m, 1H), 7.06(m, 1H), 5.27(s, 2H), 4.82(br s, 2H), 4.68(m, 1H), 3.65(m, 1H), 3.90(m, 2H), 2.70 2.40 (m, 1H), 1.97(m, 1H), 1.15(d, 3H), 0.99(d, 3H)	487
I-230		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.19	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.66(s, 1H), 7.57(d, J=6.8 Hz, 1H), 7.45(m, 2H), 7.36(d, J=1.7 Hz, 1H), 7.20(m, 1H), 7.06(m, 1H), 5.27(s, 2H), 4.78(br s, 2H), 4.42(m, 1H), 1H), 3.45(m, 2H), 2.68 (m, 4H), 2.2–1.5(m, 10H)	527
I-231		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.128	see examples	(300 MHz, $CDCl_3$) δ 7.96(s, 1H), 7.68(d, J=7.4 Hz, 1H), 7.59(m, 1H), 7.44(m, 2H), 7.36(s, 1H), 7.20(m, 1H), 7.06(m, 1H), 5.27(s, 2H), 4.80(br s, 2H), 3.90(m, 1H), 3.61(m, 2H), 3.41(m, 1H), 2.77 (m, 1H), 2.32 (s, 3H), 2.22(s, 3H), 2.10(m, 1H), 1.82(m, 1H)	487

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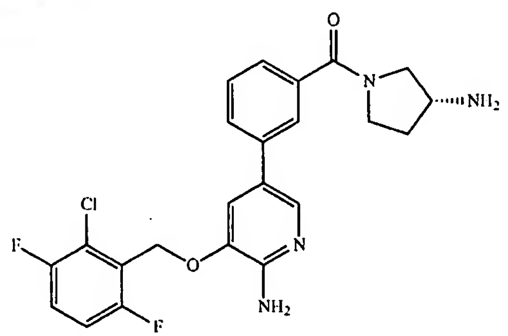
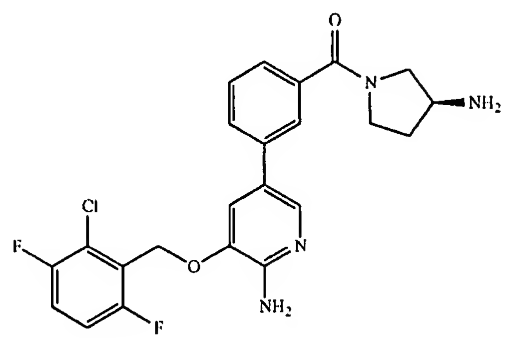
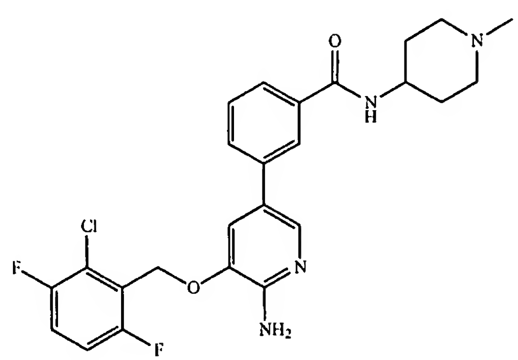
I-232		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone	0.12	see examples	(300 MHz, CD_3OD) δ 7.86(s, 1H), 7.75(m, 2H), 7.58(m, 3H), 7.38(m, 1H), 7.22(m, 1H), 5.38(s, 2H), 4.00–3.56(m, 5H, 2.40(m, 1H), 2.12 (m, 1H)	459
I-233		{3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-[(3S)-amino-pyrrolidin-1-yl]-methyanone	0.12	see examples	(300 MHz, CD_3OD) δ 7.86(s, 1H), 7.75(m, 2H), 7.58(m, 3H), 7.38(m, 1H), 7.22(m, 1H), 5.38(s, 2H), 4.00–3.56(m, 5H), 2.40(m, 1H), 2.12 (m, 1H).	459
I-234		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	0.23	see examples	(300 MHz, $CDCl_3$) δ 7.96(d, J=1.7 Hz, 1H), 7.94(s, 1H), 7.64(m, 2H), 7.47(t, J=7.7 Hz, 1H), 7.37(d, J=1.7 Hz, 1H), 7.20(m, 1H), 7.06(m, 1H), 6.25(m, 1H), 5.27(s, 2H), 4.81(br s, 2H), 3.99 (m, 1H), 2.84(m, 2H), 2.30(s, 3H), 2.16(m, 2H), 2.04 (m, 2H), 1.64(m, 2H)	487

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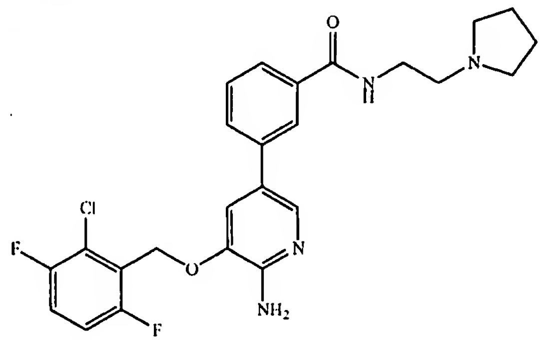
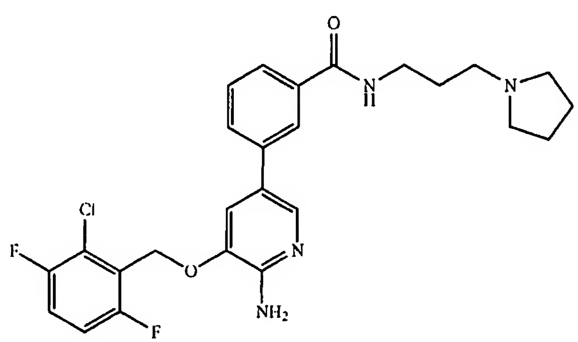
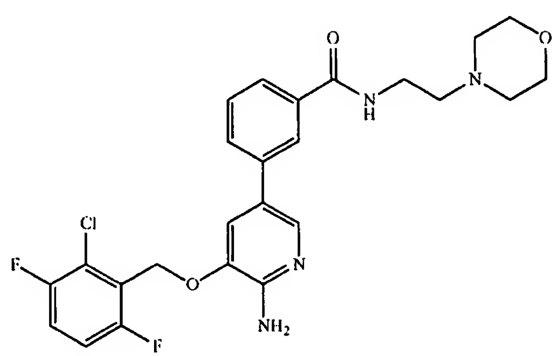
I-235		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.26	see examples	(300 MHz, $CDCl_3$) δ 8.02(s, 1H), 7.96(d, J=1.7 Hz, 1H), 7.72(d, J=7.7 Hz, 1H), 7.64(d, J=7.8 Hz, 1H), 7.47(t, J=7.7 Hz, 1H), 7.40(d, J=1.7 Hz, 1H), 7.20(m, 2H), 7.06(m, 1H), 5.27(s, 2H), 4.83(br s, 2H), 3.61(m, 2H), 2.77 (m, 2H), 2.62(m, 4H), 1.81(m, 4H)	487
I-236		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.28	see examples	(300 MHz, $CDCl_3$) δ 8.78(m, 1H), 8.04(d, J=1.6 Hz, 1H), 7.98(d, J=1.6 Hz, 1H), 7.68(d, J=7.7 Hz, 1H), 7.63(d, J=7.9 Hz, 1H), 7.45(t, J=7.7 Hz, 1H), 7.43(d, J=1.6 Hz, 1H), 7.20(m, 1H), 7.06(m, 1H), 5.29(s, 2H), 4.77 (br s, 2H), 3.61(m, 2H), 2.77(m, 2H), 2.66(m, 4H), 1.87 (m, 2H), 1.80(m, 4H)	501
I-237		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	0.35	see examples	(300 MHz, $CDCl_3$) δ 7.99(t, J=1.5 Hz, 1H), 7.97(d, J=1.8 Hz, 1H), 7.66(m, 2H), 7.49(t, J=7.7 Hz, 1H), 7.38(d, J=1.8 Hz, 1H), 7.20(m, 1H), 7.06(m, 2H), 5.27(s, 2H), 4.85(br s, 2H), 3.72(m, 4H), 3.59(m, 2H), 2.63(m, 2H), 2.52 (m, 4H)	503

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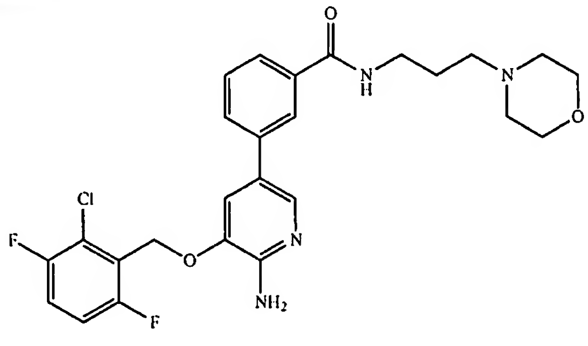
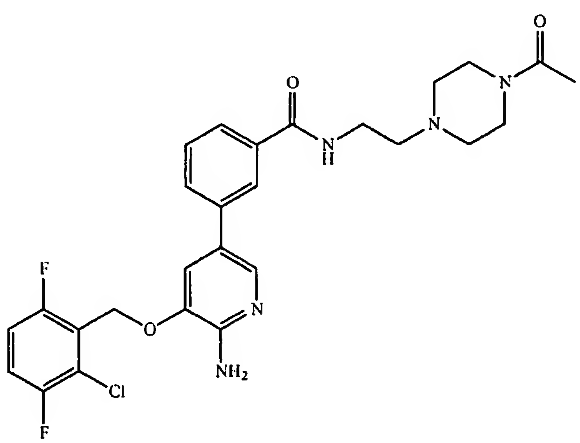
I-238		3-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	0.35	see examples	(300 MHz, $CDCl_3$) δ 8.02(m, 2H), 7.97(d, J=1.8 Hz, 1H), 7.68(d, J=7.8 Hz, 1H), 7.65(d, J=8.3 Hz, 1H), 7.48(t, J=7.7 Hz, 1H), 7.38(d, J=1.8 Hz, 1H), 7.19(m, 1H), 7.06(m, 1H), 5.27(s, 2H), 4.81(br s, 2H), 3.66(m, 4H), 3.59(m, 2H), 2.55 (m, 2H), 2.49(m, 4H), 1.81 (m, 2H)	517
I-239		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-benzamide	0.1	see examples	(300 MHz, $CDCl_3$) δ 8.00(s, 1H), 7.86(s, 1H), 7.67(dd, 2H), 7.56(t, 1H), 7.48(s, 1H), 7.21(m, 1H), 7.08(m, 1H), 6.02(br s, 2H), 5.39(s, 2H), 3.75(m, 4H), 3.60(m, 2H), 2.79(m, 2H), 2.60 (m, 4H), 2.11(s, 3H)	544

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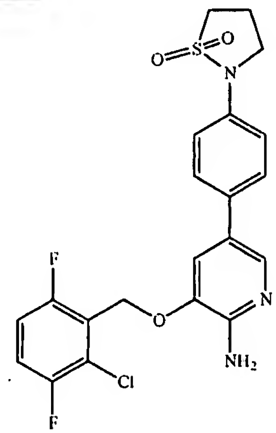
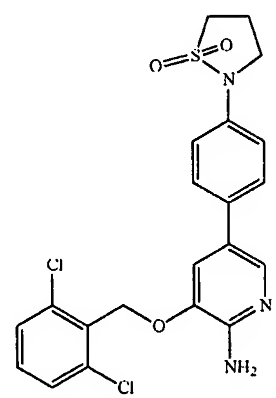
I-240		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-[4-(1,1-dioxo-1λ⁶-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine	0.1	see examples	(400 MHz, DMSO-d_6) δ 7.88(s, 1H), 7.62(d, 2H), 7.56(m, 1H), 7.51(s, 1H), 7.40(m, 1H), 7.23(d, 2H), 5.70(s, 2H), 5.28(s, 2H), 3.76(t, 2H), 3.49 (t, 2H), 2.41(t, 2H)	466
I-241		3-(2,6-Dichloro-benzyloxy)-4-[4-(1,1-dioxo-1λ⁶-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine	0.067	see examples		464

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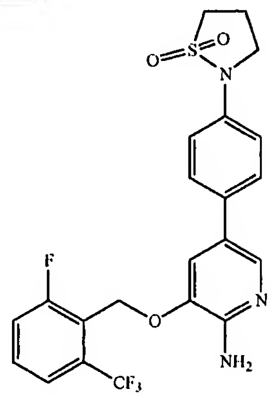
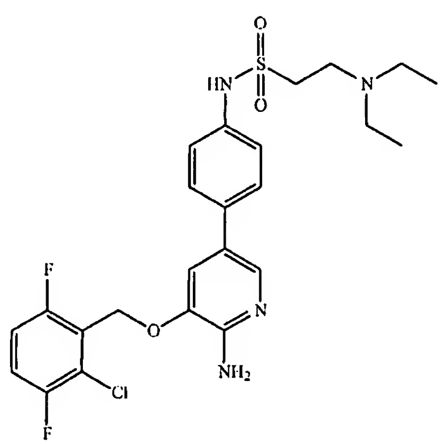
I-242		5-[4-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-3-(2-fluoro-6-trifluoromethyl-benzyloxy)-pyridin-2-ylamine	0.14	see examples		482
I-243		2-Diethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amine	0.043	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.4 Hz, 2H), 7.31(d, J=1.8 Hz, 1H), 7.24(m, 3H), 7.20(m, 1H), 7.07(m, 1H), 5.28(s, 2H), 4.70(br s, 2H), 3.22(t, J=6.1 Hz, 2H), 3.04 (t, J=6.1 Hz, 2H), 2.65 (q, J=7.1 Hz, 4H), 1.10 (t, J=7.1 Hz, 6H)	525

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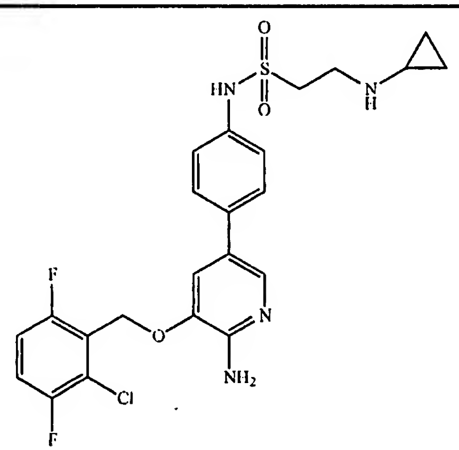
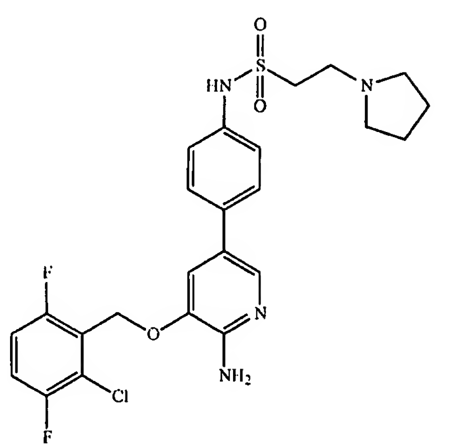
I-244		2-Cydopropylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.081	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.4 Hz, 2H), 7.31 (d, J=1.8 Hz, 1H), 7.24(m, 3H), 7.20(m, 1H), 7.07(m, 1H), 5.28(s, 2H), 4.75(br s, 2H), 3.25(s, 4H), 2.17(m, 1H), 0.9(m, 1H), 0.50(m, 2H), 0.40(m, 2H)	509
I-245		2-Pyrrolidin-1-yl-ethanesulfonic acid {4-]6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.082	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.5 Hz, 2H), 7.31 (d, J=1.8 Hz, 1H), 7.24(m, 3H), 7.20(m, 1H), 7.07(m, 1H), 5.28(s, 2H), 4.72(br s, 2H), 3.27(m, 2H), 3.06(m, 2H), 2.59 (m, 4H), 1.86(m, 4H)	523

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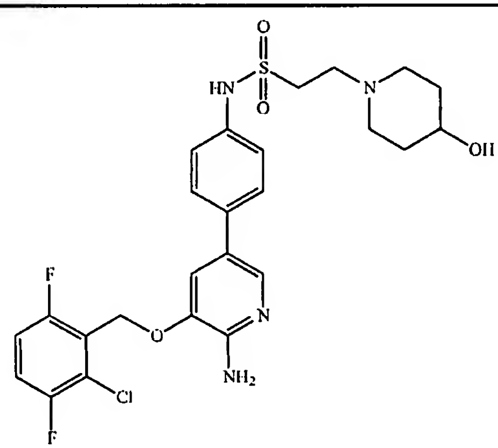
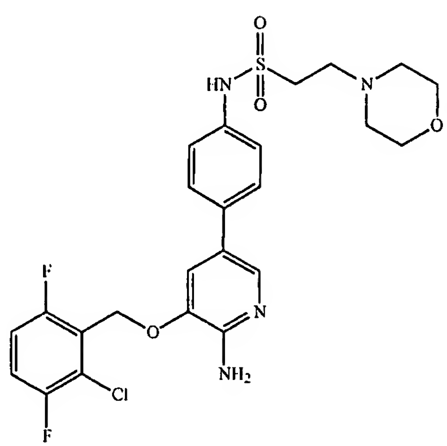
I-246		2-(4-Hydoxy-piperidin-1-yl)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.135	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.5 Hz, 2H), 7.32 (m, 2H), 7.24(m, 2H), 7.20(m, 1H), 7.07(m, 1H), 5.28(s, 2H), 4.74 (br s, 2H), 3.81(m, 1H), 3.31(t, 2H), 2.98(t, 2H) 2.85(m, 2H), 2.32(m, 2H), 1.98(m, 2H), 1.68(m, 3H)	553
I-247		2-Morpholin-4-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.31	see examples	(300 MHz, DMSO-d_6) δ 9.80(br s, 1H), 7.89(d, J=1.6 Hz, 1H), 7.59(m, 3H), 7.52 (d, J=1.6 Hz, 1H), 7.26(d, J=8.6 Hz, 2H), 5.72(br s, 2H), 5.28(s, 2H), 3.49 (m, 4H), 3.28(t, 2H), 2.69(t, 2H), 2.31(m, 4H)	539

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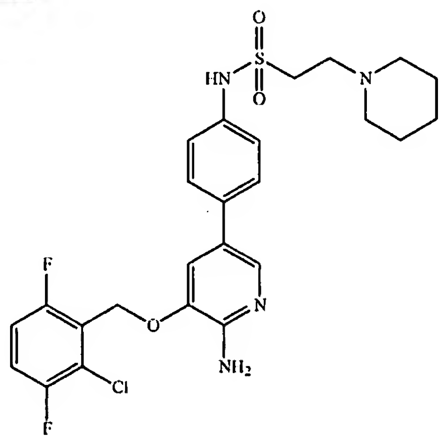
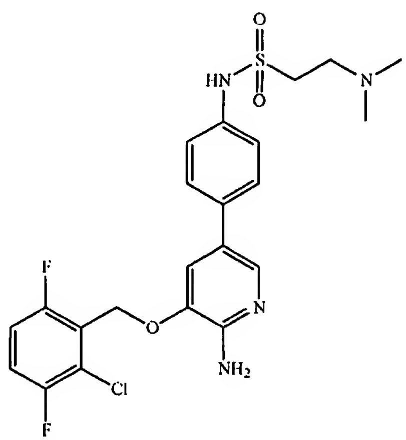
I-248		2-Pipendin-1-yl-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.114	see examples	(300 MHz, $CDCl_3$) δ 7.93(d, J=1.8 Hz, 1H), 7.48(d, J=8.5 Hz, 2H), 7.30 (m, 2H), 7.24(m, 2H), 7.20(m, 1H), 7.07 (m, 1H), 5.28(s, 2H), 4.70(br s, 2H), 3.25(t, 2H), 2.92(t, 2H), 2.52 (m, 4H), 1.85(m, 4H), 1.63(m, 2H)	537
I-249		2-Dimethylamino-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.098	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.5 Hz, 2H), 7.30 (m, 2H), 7.24(m, 2H), 7.20(m, 1H), 7.07 (m, 1H), 5.28(s, 2H), 4.71(br s, 2H), 3.20(t, 2H), 2.88(t, 2H), 2.32 (s, 6H)	497

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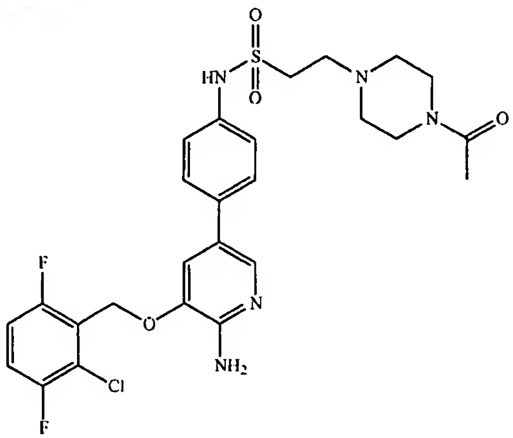
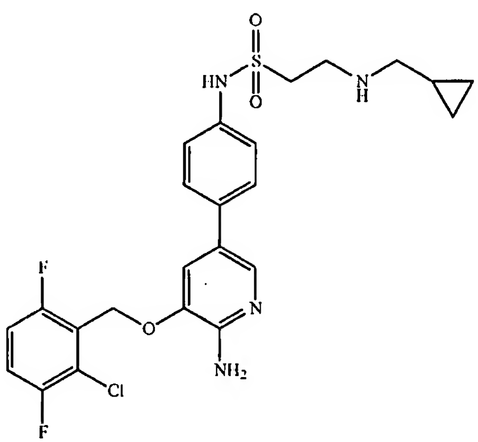
I-250		2-(4-Acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.42	see examples	(300 MHz, $CDCl_3$) δ 7.92(d, J=1.8 Hz, 1H), 7.48(d, J=8.5 Hz, 2H), 7.30 (m, 2H), 7.24(m, 1H), 7.20(m, 1H), 7.07 (m, 2H), 5.28(s, 2H), 4.80(br s, 2H), 3.65(m, 2H), 3.48(m, 2H), 3.32 (t, 2H), 2.94(t, 2H), 2.50 (m, 2H), 2.46(m, 2H), 2.10(s, 3H)	580
I-251		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.075	see examples	(300 MHz, $CDCl_3$) δ 7.94(s, 1H), 7.48(m, 2H), 7.31(m, 3H), 7.21(m, 1H), 7.18(m, 1H), 5.28(s, 2H), 4.75(s, 2H), 3.23(m, 4H), 2.58(m, 2H), 1.00(m, 1H), 0.58(m, 2H), 0.18(m, 2H)	523

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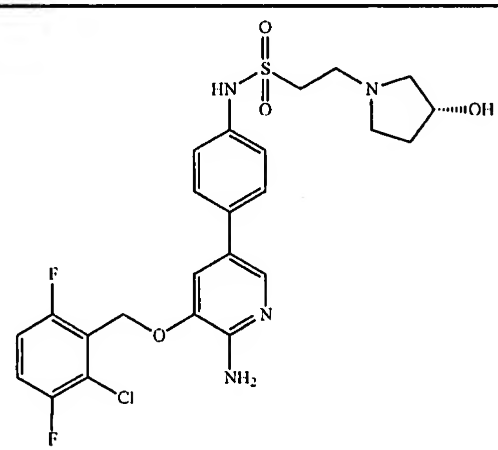
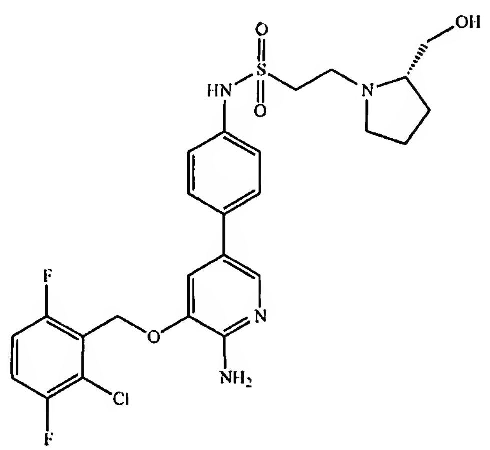
I-252		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.125	see examples	(300 MHz, $CDCl_3$) δ 7.92(s, 1H), 7.43(m, 2H), 7.31(m, 3H), 7.19(m, 1H), 7.05(m, 1H), 5.28(s, 2H), 4.75(s, 2H), 4.45(m, 1H), 3.29(m, 2H), 3.10(m, 3H), 2.88(m, 1H), 2.61(m, 1H), 2.30 (m, 2H), 1.89(m, 2H)	539
I-253		2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.097	see examples	(300 MHz, $CDCl_3$) δ 7.89(s, 1H), 7.45(m, 2H), 7.30(m, 3H), 7.21(m, 1H), 7.08(m, 1H), 5.31(s, 2H), 4.78(s, 2H), 3.55(m, 2H), 3.36(t, 1H), 3.11(m, 2H), 2.69(m, 2H), 2.21(m, 1H), 1.89 (m, 6H)	553

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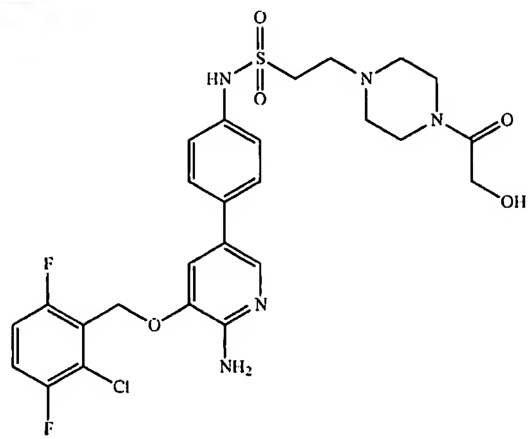
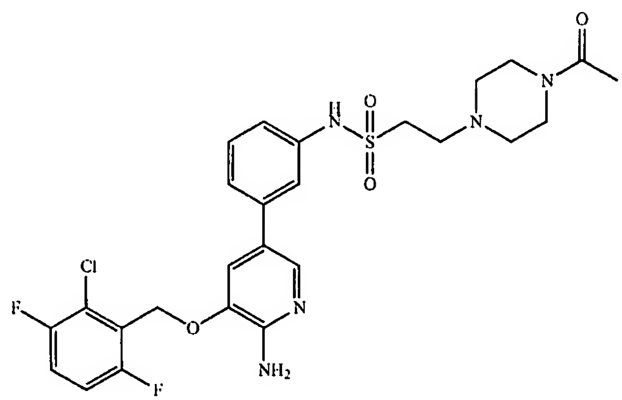
I-254		2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {4-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin 3-yl]-phenyl}-amide	0.18	see examples	(300 MHz, DMSO-d_6) δ 9.81(s, 1H), 7.89 (s, 1H), 7.58(d, 2H), 7.50(s, 1H), 7.39(m, 2H), 7.24(d, 2H), 5.75(s, 2H), 5.28(s, 2H), 4.54(t, 1H), 4.01(d, 2H), 3.29(m, 6H), 2.79(t, 2H), 2.36(m, 4H)	596
I-255		2-(4-Acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.68	see examples	(300 MHz, $CDCl_3$) δ 2.02(s, 3H), 2.30 (m, 4H), 2.95(m, 4H), 3.35(m, 4H), 3.55(m, 2H), 5.30(d, 2H), 5.42(s, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.35(m, 5H), 8.00(d, 1H), 10.17(s, 1H)	580

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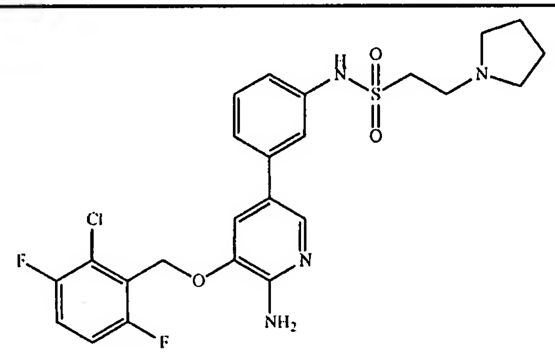
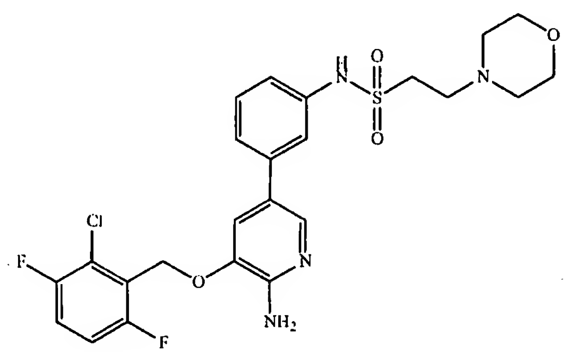
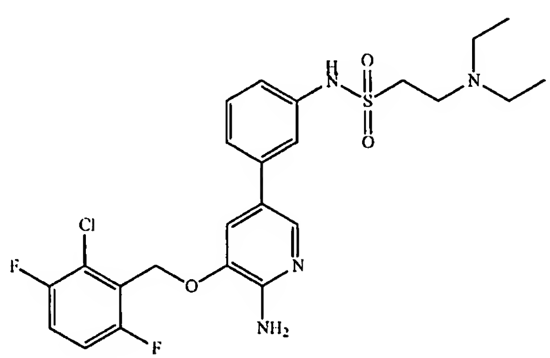
I-256		2-Pyrrolidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.23	see examples	(300 MHz, $CDCl_3$) δ 1.60–1.80(m, 4H), 2.40–2.55(m, 4H), 3.02(t, J=6.6 Hz, 2H), 3.29(t, J=6.6 Hz, 2H), 5.08(s, 2H), 5.29(d, J=1.3 Hz, 2H), 6.95–7.05 (m, 1H), 7.10–7.20 (m, 1H), 7.25–7.45(m, 5H), 7.97(d, J=1.7 Hz, 1H)	524
I-257		2-Morpholin-4-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.64	see examples	(300 MHz, $CDCl_3$) δ 2.42(t, J=4.6 Hz, 4H), 2.90(t, J=6.9 Hz, 2H), 3.31(t, J=6.9 Hz, 2H), 3.62(t, J=4.6 Hz, 4H), 5.24(s, 2H), 5.30(d, J=1.3 Hz, 2H), 6.95–7.05(m, 1H), 7.10–7.20(m, 1H), 7.30–7.45(m, 5H), 7.99(d, J=1.6 Hz, 1H), 9.38 (s, 1H)	540
I-258		2-Diethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}amide	1.67	see examples	(300 MHz, $CDCl_3$) δ 1.00(t, 6H), 2.52(q, 4H), 3.02(t, 2H), 3.25(t, 2H), 5.19(s, 2H), 5.29(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.35(m, 5H), 7.98(d, 1H)	526

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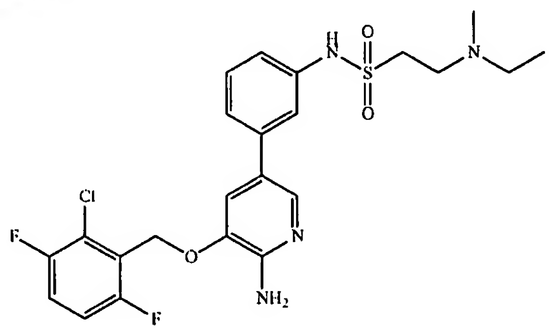
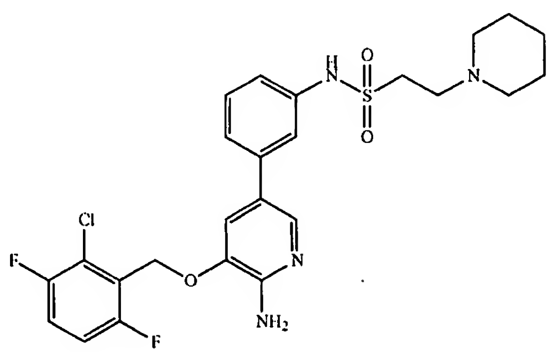
I-259		2-Dimethylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.5	see examples	(300 MHz, $CDCl_3$) δ 2.24(s, 6H), 2.85(t, 2H), 3.24(t, 2H), 5.11(s, 2H), 5.29(d, 2H), 7.07(m, 1H), 7.15(m, 1H), 7.35(m, 5H), 7.98(d, 1H)	498
I-260		2-Piperidin-1-yl-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.63	see examples	(300 MHz, $CDCl_3$) δ 1.30-1.60(m, 6H), 2.30–2.45(m 4H), 2.89(t, J=6.7 Hz, 2H), 3.28(t, J=6.7 Hz, 2H), 5.13(s, 2H), 5.29(d, J=1.4 Hz, 2H), 6.95–7.05 (m, 1H), 7.15–7.45(m, 6H), 7.98(d, J=1.6 Hz, 1H)	538

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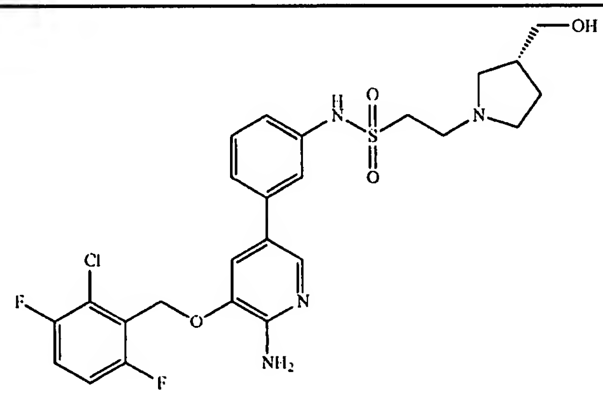
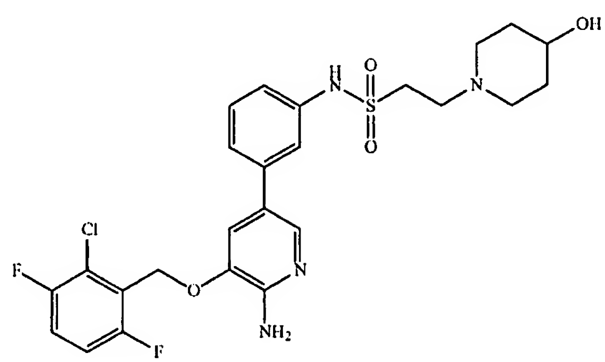
I-261		2-[(3R)-3-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.7	see examples	(300 MHz, $CDCl_3$) δ 1.60–1.8(m, 4H), 2.05–2.15(m, 1H), 2.55–2.75(m, 2H), 2.95–3.15(m, 2H), 3.25–3.55(m, 3H), 3.82(dd, J=3.0. 11.2 Hz, 1H), 4.97 (s, 2H), 5.28(d, J=1.6 Hz, 2H), 6.98–7.08 (m, 1H), 7.10–7.20 (m, 1H), 7.25–7.45(m, 5H), 7.98(d, J=1.8 Hz, 1H)	554
I-262		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.5	see examples	(300 MHz, DMSO-d_6) δ 1.15–1.30(m, 2H), 1.45–1.55(m, 2H), 1.90–2.02(m, 2H), 2.50–2.70(m, 4H), 4.49(brs, 1H), 5.28(s, 2H), 5.82(s, 2H), 7.05–7.10(m, 1H), 7.20–7.40(m, 5H), 7.45–7.60(m, 1H), 7.83(d, J=1.6 Hz, 1H)	554

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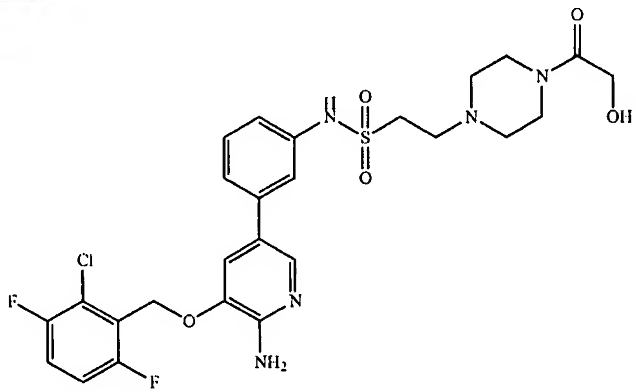
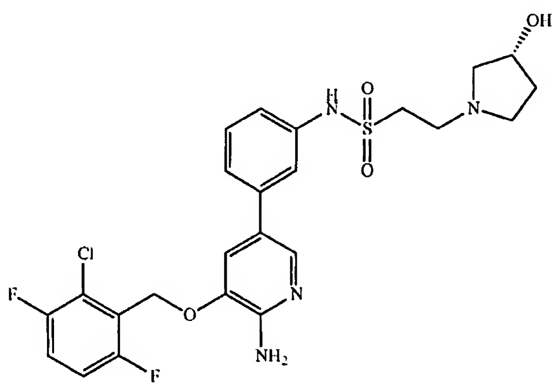
I-263		2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.14	see examples	(300 MHz, $CDCl_3$) δ 2.36(m, 4H), 2.92(t, 2H), 3.14(m, 2H), 3.32(t, 2H), 3.54(m, 2H), 3.60(br s, 1H), 4.07(s, 2H), 5.30(s, 2H), 5.40(br s, 2H), 7.06(m, 1H), 7.24(m, 2H), 7.34(m, 2H), 7.44(m, 2H), 7.99 (d, J=1.6 Hz, 1H), 9.88(br s, 1H)	596
I-264		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1.097	see examples	(300 MHz, $CDCl_3$) δ 1.65(m, 1H), 2.08(m, 1H), 2.22(m, 1H), 2.46(m, 1H), 2.76(m, 1H), 2.87(m, 1H), 3.02(m, 2H), 3.32(m, 2H), 4.28(m, 1H), 5.28(br s, 2H) 5.29(s, 2H), 7.06(m, 1H), 7.24(m, 2H), 7.44(m, 5H), 8.00(d, J= 1.7 Hz, 1H)	539

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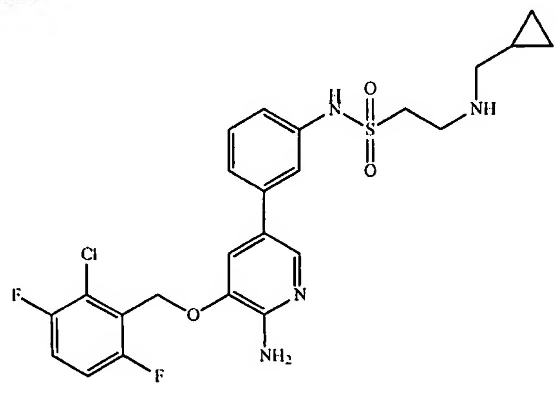
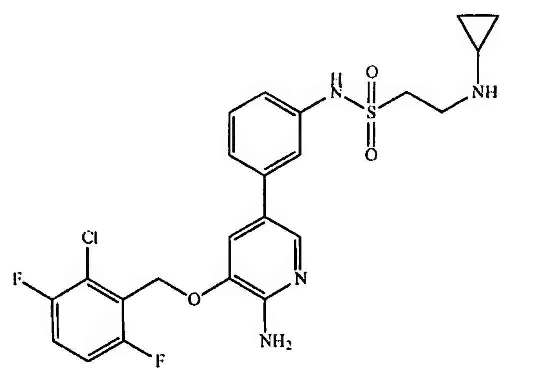
I-265		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	1	see examples	(300 MHz, $CDCl_3$) δ 0.02(m, 2H), 0.39(m, 2H), 0.84(m, 1H), 2.40(d, 2H), 3.14(t, 2H), 3.32(t, 2H), 5.28(s, 2H), 5.38(br s, 2H), 7.06(m, 1H), 7.24(m, 2H), 7.44(m, 5H), 8.00(d, J=1.7 Hz, 1H)	523
I-266		2-Cyclopropylamino-ethanesulfonic acid {3-[6-amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-amide	0.9	see examples	(300 MHz, $CDCl_3$) δ 0.28(m, 2H), 0.37(m, 2H), 2.06(m, 1H), 3.15–3.40 (m, 4H), 5.30(d, 2H), 5.39(s, 2H), 7.07(m, 1H), 7.19(m, 1H), 7.30–7.55(m, 5H), 8.01(d, 1H)	509

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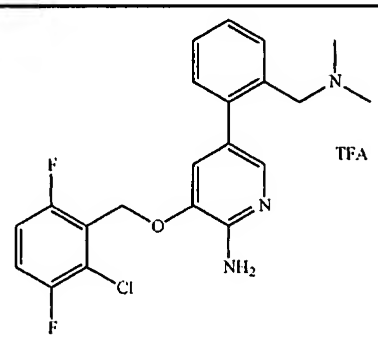
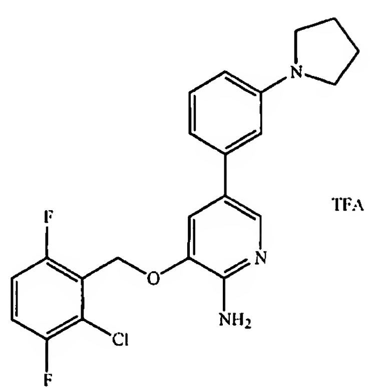
I-267		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(2-dimethylaminomethyl-phenyl)-pyridin-2-ylamine; compound with trifluoro-acetic acid		see examples		404
I-268		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-yl-phenyl)-pyridin-2-ylamine; compound with trifluoro-acetic acid	4	see examples	(400 MHz, DMSO-d_6) δ 1.94(t, 4H), 3.31 (t, 4H), 5.44(s, 2H), 6.56(d, 1H), 6.74(s, 1H), 6.88(d, 1H), 7.24(t, 1H), 7.43(m, 1H), 7.58(m, 3H), 7.83(m, 2H)	416

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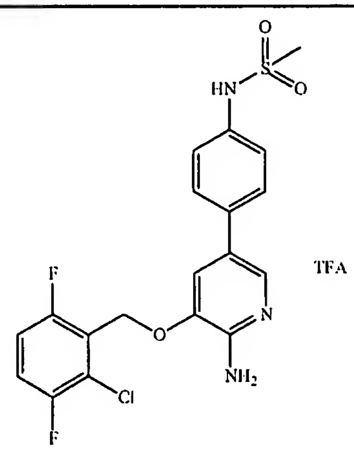
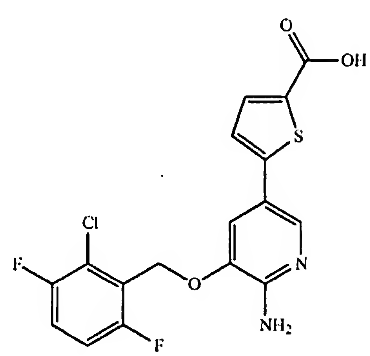
I-269		N-{4-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide; compound with trifluoro-acetic acid	see examples	(400 MHz, DMSO-d_6) δ 2.99(s, 3H), 5.35 (s, 2H), 6.72(br s, 2H), 7.27(d, 2H), 7.42(m, 1H), 7.59(m, 1H), 7.65(d, 2H), 7.73(s, 1H), 7.84(s, 1H), 9.79(s, 1H)	440
I-270		5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid	see examples		397

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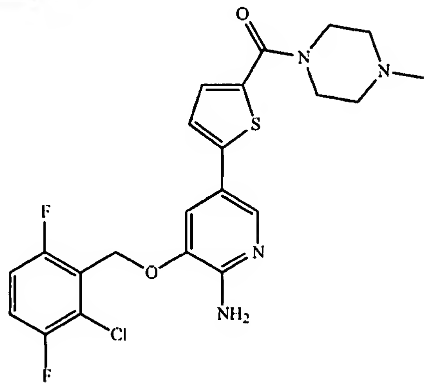
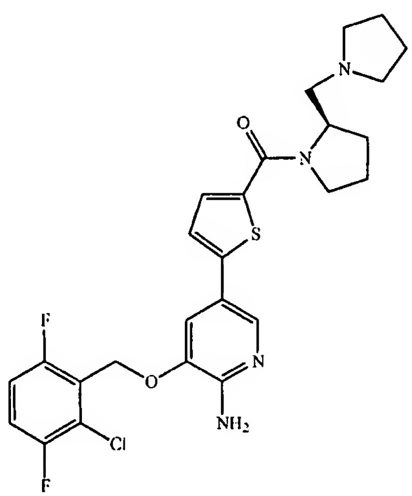
I-271		{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.8 Hz, 1H), 7.30(d, J=1.8 Hz, 1H), 7.25(d, J=1.5 Hz, 1H), 7.20(m, 1H), 7.10(d, J=3.8 Hz, 1H), 7.07 (m, 1H), 5.27(d, J=1.7 Hz, 2H), 4.82(br s, 2H), 3.81(m, 4H), 2.47(m, 4H), 2.34(s, 3H)	479
I-272		{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	see examples	(300 MHz, $CDCl_3$) δ 8.02(d, J=1.8 Hz, 1H), 7.52(m, 1H), 7.32(d, J=1.8 Hz, 1H), 7.21(m, 1H), 7.14(d, J=3.9 Hz, 1H), 7.07(m, 1H), 5.27(d, J=1.5 Hz, 2H), 4.80(br s, 2H), 4.50(m, 1H), 3.81(m, 2H), 2.74(m, 4H), 2.25–1.82(m, 10H).	533

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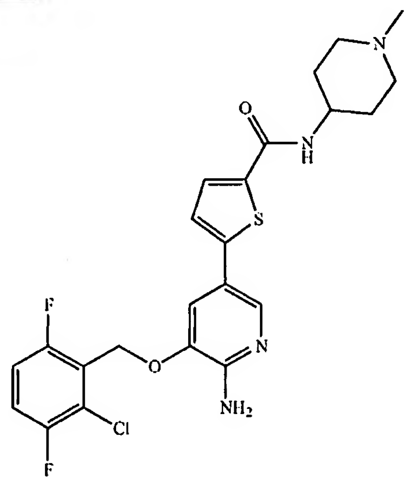
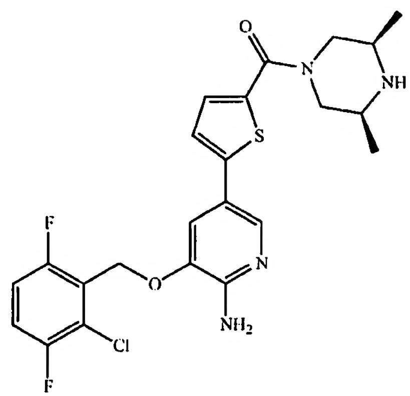
I-273		5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (1-methyl-piperidin-4-yl)-amide	see examples	(300 MHz, $CDCl_3$) δ 8.02(d, J=1.8 Hz, 1H), 7.42(d, J=3.9 Hz, 1H), 7.29(d, J=1.8 Hz, 1H), 7.21(m, 1H), 7.15(d, J=3.9 Hz, 1H), 7.07(m, 1H), 5.89(br d, 1H), 5.29(d, J=1.5 Hz, 2H), 4.82(br s, 2H), 4.05(m, 1H), 3.05(m, 2H), 2.50(s, 3H), 2.40 (m, 2H), 1.85(m, 2H), 1.62(m, 2H)	493
I-274		{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(3,5-dimethyl-piperazin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.8 Hz, 1H), 7.30(d, J=1.8 Hz, 1H), 7.24(d, J=3.8 Hz, 1H), 7.21(m, 1H), 7.10(d, J=3.8 Hz, 1H), 7.07(m, 1H), 5.28(d, J=1.5 Hz, 2H), 4.82(br s, 2H), 4.38(m, 2H), 2.98 (m, 2H), 2.65 (m, 2H), 1.68(br s, 1H), 1.11(d, J=6.2 Hz, 6H)	493

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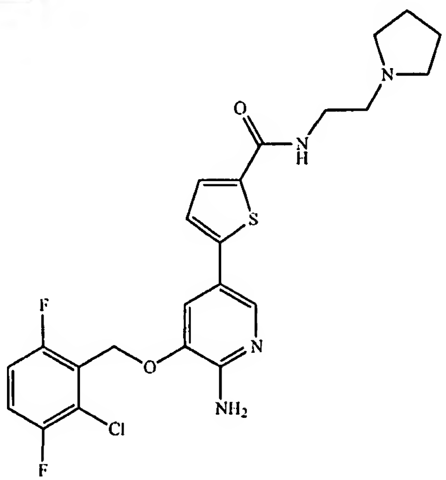
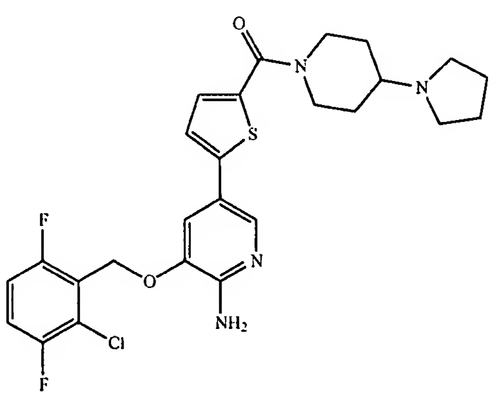
I-275		5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophene-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide	see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.8 Hz, 1H), 7.82(br m, 1H), 7.66(d, J=3.9 Hz, 1H), 7.29(d, J=1.8 Hz, 1H), 7.21(m, 1H), 7.11(d, J=3.9 Hz, 1H), 7.07 (m, 1H), 5.26(d, J=1.5 Hz, 2H), 4.81(br s, 2H), 3.71(m, 2H), 3.02 (m, 2H), 2.95(m, 2H), 2.01(m, 4H), 1.97(m, 2H), 1.11(d, J= 6.2 Hz, 6H)	493
I-276		{5-[6-Amino-5-(2-chloro-3,6-difluoro-benzyloxy)-pyridin-3-yl]-thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.8 Hz, 1H), 7.29(d, J=1.8 Hz, 1H), 7.24 (d, J=3.8 Hz, 1H), 7.20(m, 1H), 7.09 (d, J=3.8 Hz, 1H), 7.07(m, 1H), 5.27(d, J=1.5 Hz, 2H), 4.80(br s, 2H), 4.43(m, 2H), 3.10(m, 2H), 2.63 (m, 4H), 2.34 (m, 1H), 1.99(m, 2H), 1.83(m, 4H), 1.63(m, 2H).	533

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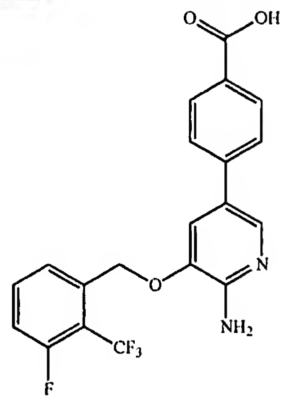
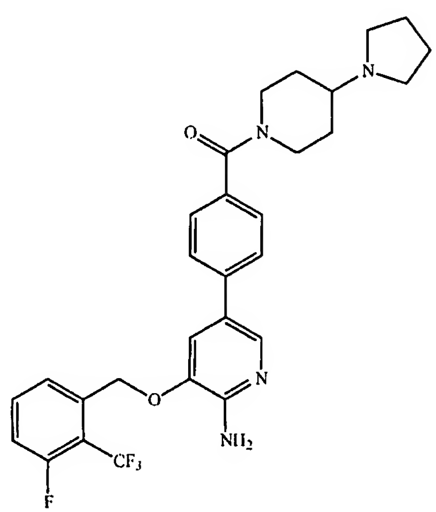
I-277		4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzoic acid	see examples		407
I-278		{4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.8 Hz, 1H), 7.61–7.42(m, 6H), 7.21(d, J=8.7 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 5.33(s, 2H), 4.81(br s, 2H), 4.62(m, 1H), 3.84(m, 1H), 2.98(m, 2H), 2.65(m, 4H), 2.32 (m, 1H), 1.97(m, 2H), 1.84(m, 4H), 1.60(m, 2H)	543

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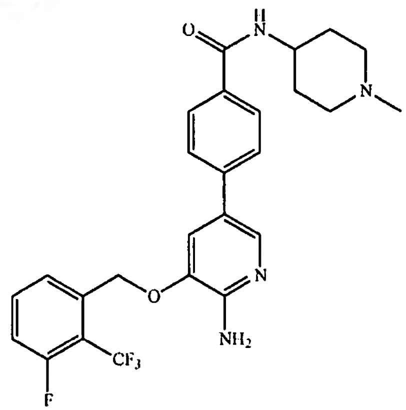
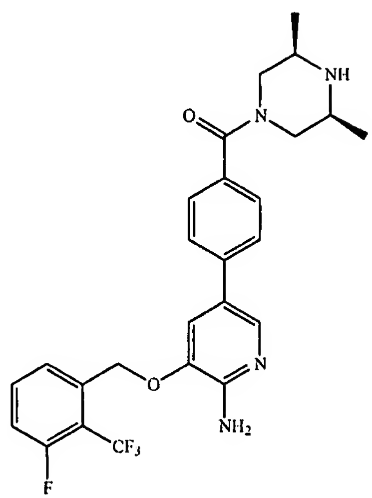
I-279		4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	see examples	(300 MHz, $CDCl_3$) δ 7.99(d, J=1.8 Hz, 1H), 7.80(d, J=8.3 Hz, 2H), 7.55(m, 1H), 7.52(d, J=8.3 Hz, 2H), 7.44(d, J=7.8 Hz, 1H), 7.22(t, J=8.7 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 5.99 (br d, 1H), 5.34(s, 2H), 4.83(br s, 2H), 4.04(m, 1H), 2.87(m, 2H), 2.34(s, 3H), 2.20(m, 2H), 2.05(m, 2H), 1.63(m, 2H)	503
I-280		{4-[-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 7.98(s, 1H), 7.61–7.43(m, 6H), 7.22(t, J=8.7 Hz, 1H), 7.13(d, J=1.6 Hz, 1H), 5.33(s, 2H), 4.82(br s, 2H), 4.65(m, 1H), 3.65 (m, 1H), 2.90(m, 2H), 2.68(m, 1H), 2.42(m, 1H), 1.60(m, 1H), 1.12 (d, 3H), 1.00(d, 3H)	503

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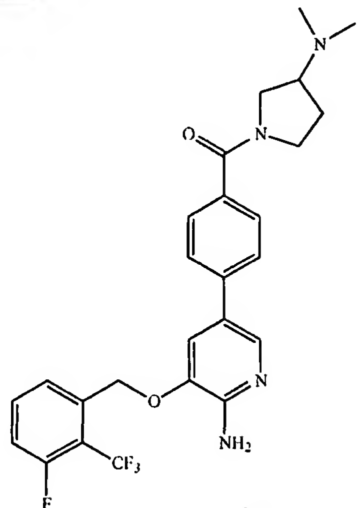
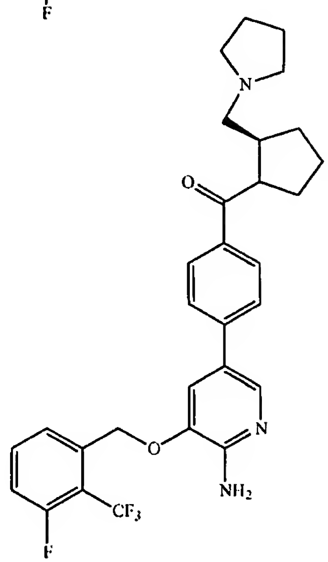
I-281		{4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3-dimethylamino-pyrrolidin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=2.4 Hz, 1H), 7.61–7.43(m, 6H), 7.21(t, J=8.8 Hz, 1H), 7.14(d, J=2.4 Hz, 1H), 5.33(s, 2H), 4.87(br s, 2H), 3.89(m, 1H), 3.65(m, 2H), 3.42(m, 1H), 2.70 (m, 1H), 2.32(s, 3H), 2.23(s, 3H), 2.14 (m, 1H), 1.82(m, 1H)	503
I-282		{4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	see examples	(300 MHz, $CDCl_3$) δ 7.98(d, J=1.4 Hz, 1H), 7.58–7.43(m, 6H), 7.20(t, J=8.8 Hz, 1H), 7.13 (d, J=1.4 Hz, 1H), 5.34(s, 2H), 4.81 (br s, 2H), 4.46(m, 1H), 3.50(m, 2H), 2.77(m, 4H), 2.30–1.50(m, 10H)	543

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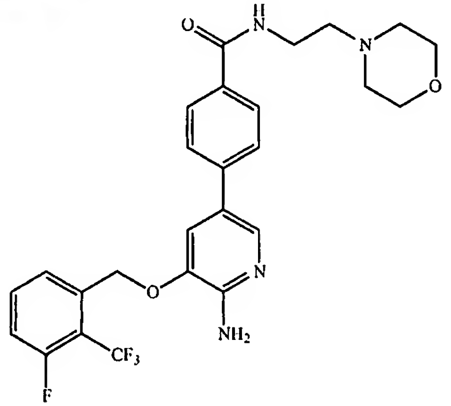
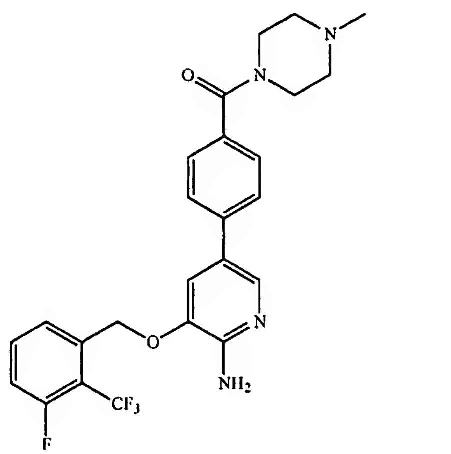
I-283		4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-#N1-(2-morpholin-4-yl-ethyl)-benzamide	see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.2 Hz, 1H), 7.83(d, J=8.2 Hz, 2H), 7.56(m, 1H), 7.55(d, J=8.2 Hz, 2H), 7.45(d, 1H), 7.20(t, J=8.8 Hz, 1H), 7.13(d, J=1.4 Hz, 1H), 6.76 (m, 1H), 5.34(s, 2H), 4.85(br s, 2H), 3.74(m, 4H), 3.56(m, 2H), 2.62(m, 2H), 2.52(m, 4H)	519
I-284		{4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	see examples	(300 MHz, $CDCl_3$) δ 7.97(d, J=1.8 Hz, 1H), 7.58-7.43(m, 6H), 7.20(t, J=8.8 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H), 5.34(s, 2H), 4.93(br s, 2H), 3.80(m, 2H), 3.56 (m, 2H), 2.44(m, 4H), 2.33(s, 3H)	489

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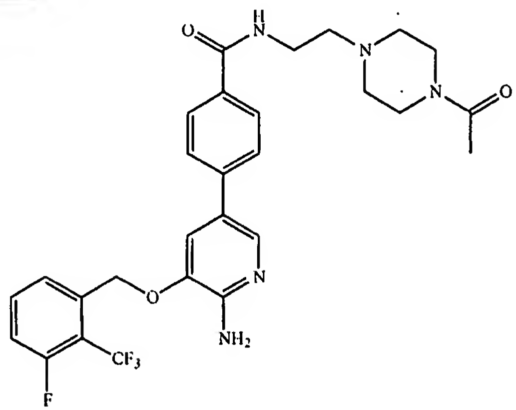
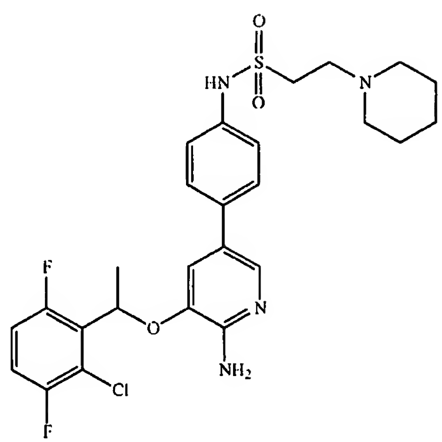
I-285		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-benzamide		see examples	(300 MHz, $CDCl_3$) δ 8.00(d, J=1.2 Hz, 1H), 7.82(d, J=8.2 Hz, 2H), 7.58(m, 1H), 7.55(d, J=8.2 Hz, 2H), 7.44 (d, J=7.8 Hz, 1H), 7.22(t, J=8.8 Hz, 1H), 7.14(d, J=1.4 Hz, 1H), 6.72(m, 1H), 5.34(s, 2H), 4.85(br s, 2H), 3.65(m, 2H), 3.60(m, 2H), 3.50(m, 2H), 2.65(m, 2H), 2.51(m, 4H), 2.10(s, 3H)	560
I-286		2-Piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2-cloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.18	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.26(d, 2H), 7.20(d, 2H), 7.06(m, 3H), 7.59(s, 1H), 4.86(s, 2H), 3.25(m, 2H), 2.89(m, 2H), 2.49(m, 4H), 1.83(d, 3H), 1.62(m, 4H), 1.48(m, 2H)	551

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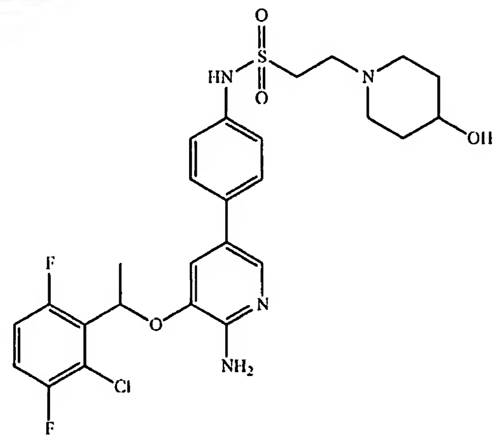
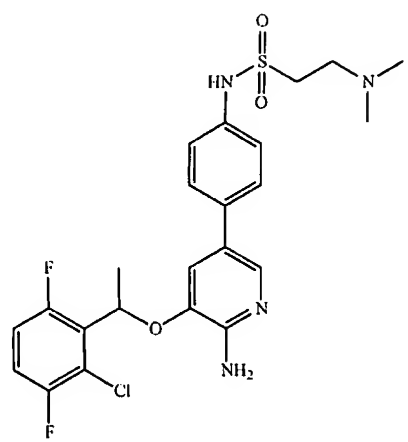
I-287		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.14	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.26(d, 2H), 7.20(d, 2H), 7.06(m, 3H), 7.59(s, 1H), 4.86(s, 2H), 3.76(m, 1H), 3.25(m, 2H), 2.89(m, 2H), 2.78(m, 2H), 2.26(m, 2H), 1.83(m, 5H), 1.62(m, 2H)	567
I-288		2-Dimiethylamino-ethanesulfonic acid (4-}6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.15	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.26(d, 2H), 7.20(d, 2H), 7.06(m, 3H), 7.59(s, 1H), 4.86(s, 2H), 3.21(m, 2H), 2.88(m, 2H), 2.30(s, 6H), 2.26(m, 2H), 1.82(d, 3H)	511

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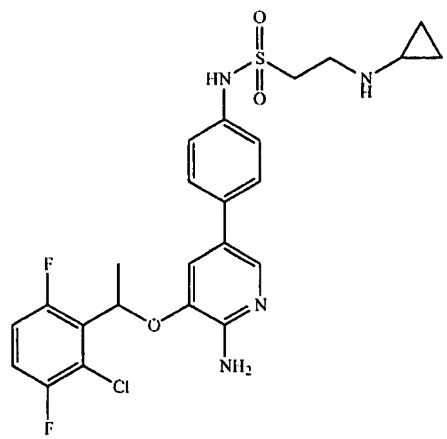
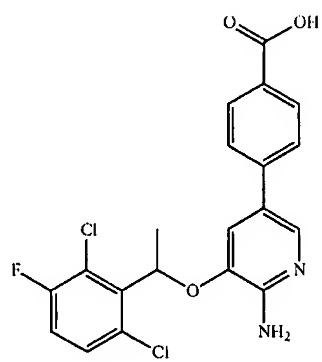
I-289		2-Cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.16	see examples	(300 MHz, $CDCl_3$) δ 7.89(s, 1H), 7.38(d, 2H), 7.26(d, 2H), 7.18(m, 3H), 5.95(m, 1H), 4.89(s, 2H), 3.22(m, 4H), 2.14(m, 1H), 1.85(d, 3H), 0.50(m, 2H), 0.38(m, 2H)	523
I-290		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		see examples		422

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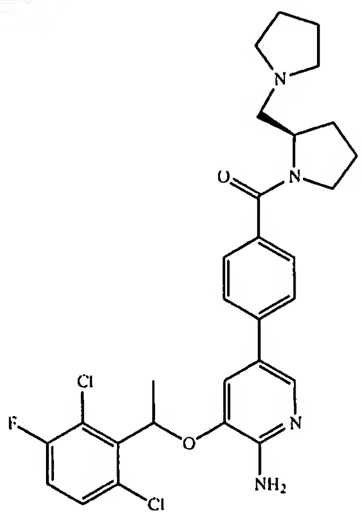
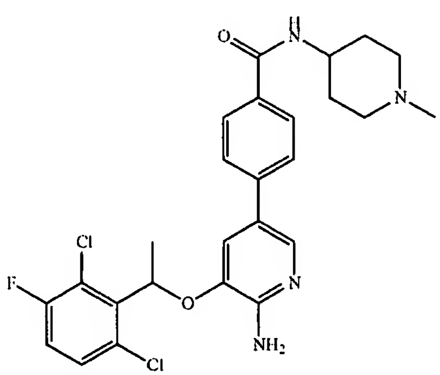
I-291		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.063	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.52(d, 2H), 7.31(d, 2H), 7.08(m, 3H), 6.13(m, 1H), 4.86(s, 2H), 4.30(m, 1H), 3.40(m, 2H), 2.60(m, 4H), 1.82(d, 3H), 1.70-2.0(m, 10H)	557
I-292		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.069	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.78(d, 2H), 7.35(d, 2H), 7.31(m, 3H), 6.16(tert, 1H), 5.90(d, 1H), 4.86(s, 2H), 4.05(m, 1H), 2.85(d, 1H), 2.35 (s, 3H), 2.05(d, 1H), 2.25(t, 1H), 1.82(d, 3H), 1.60 (m, 1H), 1.29(m, 2H), 0.86(m, 2H)	559

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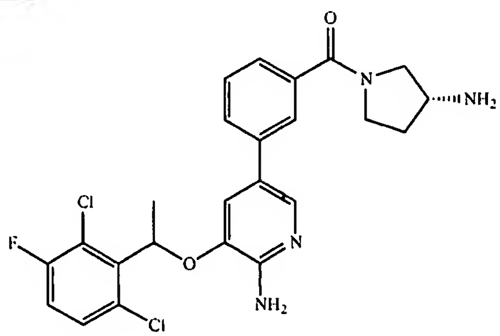
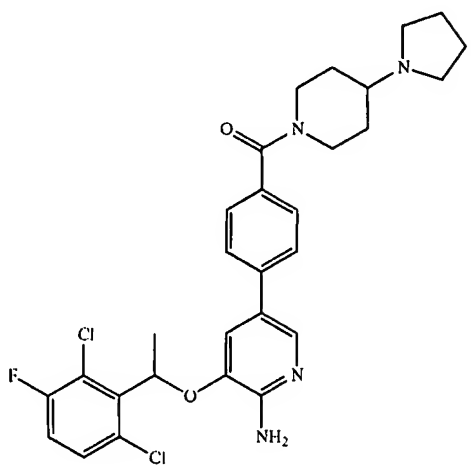
I-293		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl)]-methanone	0.051	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.51(s, 1H), 7.38(m, 3H), 7.30(m, 1H), 7.15(m, 1H), 6.97(s, 1H), 6.15(m, 1H), 4.94(s, 2H), 3.45–3.89(m, 4H), 3.20 (m, 1H), 2.25(m, 1H), 2.15(m, 1H), 1.82(d, 3H), 1.34(m, 2H)	489
I-294		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.062	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.70(m, 1H), 7.45(m, 1H), 7.30(s, 2H), 7.08(t, 1H), 6.92(d, 2H), 6.13(m, 1H), 4.86(s, 2H), 4.30(t, 1H), 2.80 (m, 4H), 1.82(d, 3H), 1.80(m, 4H), 1.35(m, 4H), 0.89(m, 4H)	559

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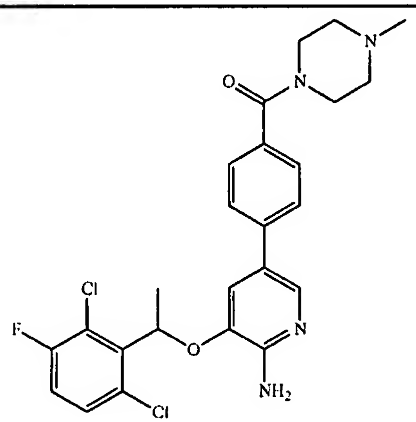
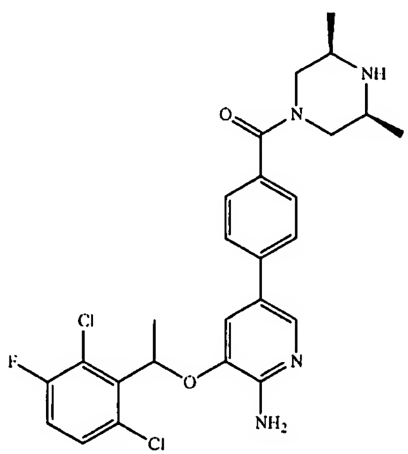
I-295		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.079	see examples	(300 MHz, $CDCl_3$) δ 7.89(s, 1H), 7.71(d, 2H), 7.49(d, 2H), 7.40(s, 1H), 7.35(m, 1H), 7.08(m, 1H), 6.17(m, 1H), 4.98(s, 2H), 4.28(t, 2H), 3.68 (m, 4H), 2.38(m, 2H), 2.31(s, 3H), 1.88(d, 3H)	503
I-296		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-methyl-piperazin-1-yl)-methanone	0.054	see examples		

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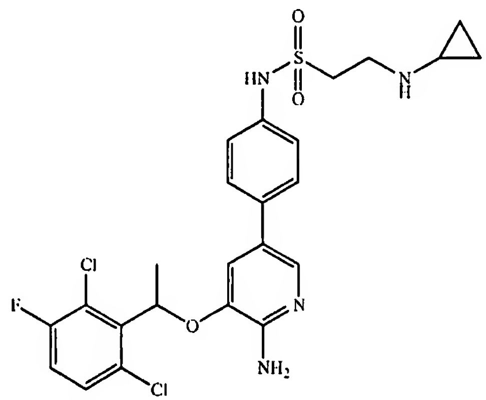
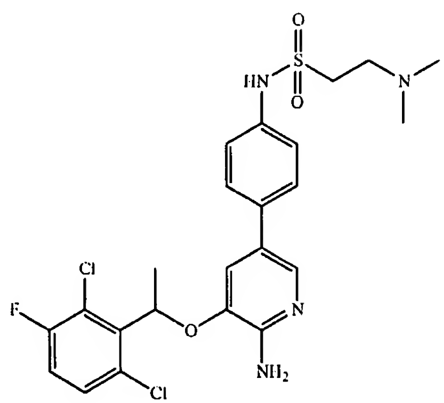
I-297		2-Cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.164	see examples	(300 MHz, $CDCl_3$) δ 7.79(s, 1H), 7.30(m, 3H), 7.24(m, 3H), 7.08(t, 1H), 6.95(s, 1H), 6.09(m, 1H), 4.89(s, 2H), 3.21(m, 4H), 2.12 (m, 1H), 1.84 (d, 3H), 0.87(m, 1H), 0.50(m, 2H), 0.36(m, 2H)	539
I-298		2-Dimethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.059	see examples	(300 MHz, $CDCl_3$) δ 7.81(s, 1H), 7.26(m, 6H), 7.04(t, 1H), 6.94(s, 1H), 6.12 (m, 1H), 4.95(s, 2H), 3.21(t, 2H), 2.85(t, 2H), 2.31(s, 6H), 1.85 (d, 3H)	527

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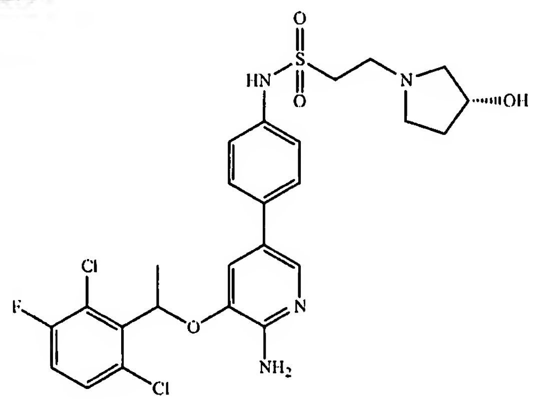
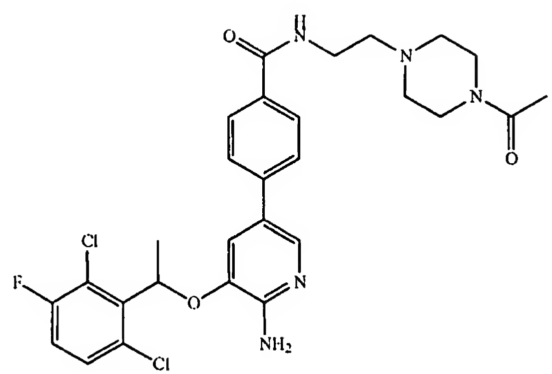
I-299		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl)]-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.062	see examples	(300 MHz, $CDCl_3$) δ 7.84(d, 1H), 7.30(m, 5H), 7.10(t, 1H), 6.89(s, 1H), 6.10(tert, 1H), 4.86(s, 2H), 4.40(s, 1H), 3.21(m, 2H), 2.88 (m, 3H), 2.67(d, 1H), 2.46(m, 1H), 2.20(m, 2H), 2.05(s, 1H), 1.85(d, 3H), 1.25(s, 1H)	570
I-300		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide	0.059	4 as in Example I-291	(300 MHz, CDCl3) δ 7.85(s, 1H), 7.79(d, 2H), 7.42(d, 2H), 7.30(dd, 1H), 7.07(t, 1H), 7.02(d, 1H), 6.81 (bm, 1H), 6.13(q, 1H), 5.42(s, 2H), 3.80(m, 2H), 3.62 (m, 2H), 3.53(m, 2H), 2.68 (m, 2H), 2.52(m, 4H), 2.10(s, 3H), 1.87(d, 3H).	575 [M + 1]

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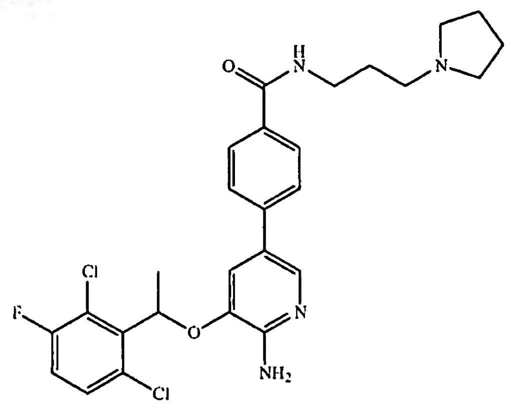
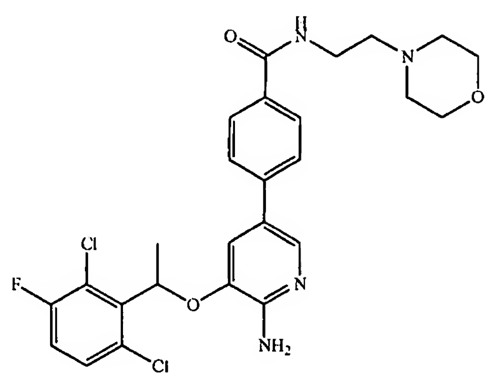
I-301		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.064	4 as in Example I-291	(300 MHz, CDCl3) δ 8.71 (bm, 1H), 7.92(m, 3H), 7.42(d, 2H), 7.31(dd, 1H), 7.06(t, 1H), 7.01(s, 1H), 6.12 (q, 1H), 4.97(s, 2H), 3.65(m, 2H), 3.00(m, 6H), 2.00 (m, 6H), 1.87(d, 3H).	533 [M + 1]
I-302		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.071	4 as in Example I-291)	(300 MHz, CDCl3) δ 7.90(d, 1H), 7.79(d, 2H), 7.44(d, 2H), 7.31(dd, 1H), 7.06(t, 1H), 7.01(d, 1H), 6.83 (bm, 1H), 6.12 (q, 1H), 5.05(s, 2H), 3.74(m, 4H), 3.58 (m, 2H), 2.63(m, 2H), (m, 4H), 1.87(d, 3H).	533 [M + 1]

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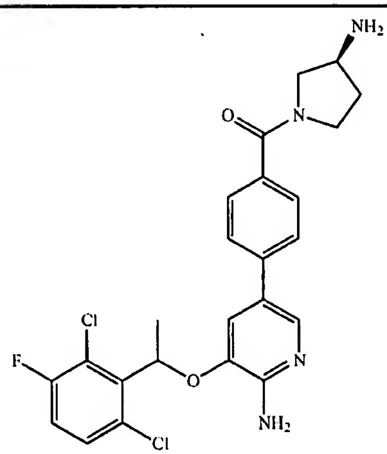
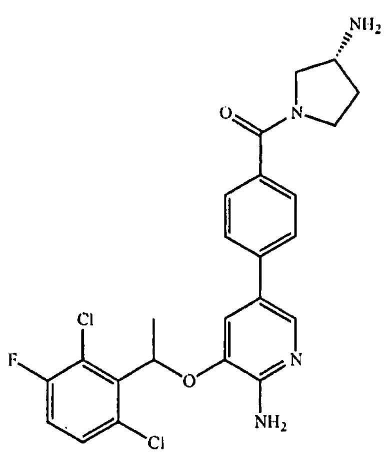
I-303		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone	0.059	4 as in Example I-291	(300 MHz, CD3OD) δ 7.76(s, 1H), 7.54(m, 1H), 7.42(m, 4H), 7.24(t, 1H), 7.04(s, 1H), 6.22(q, 1H), 4.82(s, 2H), 3.76(m, 1H), 3.68(m, 2H), 3.52(m, 1H), 2.28(m, 1H), 1.92(m, 3H), 1.75(m, 1H), 1.42 (m, 1H).	491 [M + 1]
I-304		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.072	4 as in Example I-291	(300 MHz, CD3OD) δ 7.76(s, 1H), 7.54(m, 1H), 7.42(m, 4H), 7.24(t, 1H), 7.04(s, 1H), 6.22(q, 1H), 4.82(s, 2H), 3.76(m, 1H), 3.68(m, 2H), 3.52(m, 1H), 2.28(m, 1H), 1.92(m, 3H), 1.75(m, 1H), 1.42 (m, 1H).	491 [M + 1]

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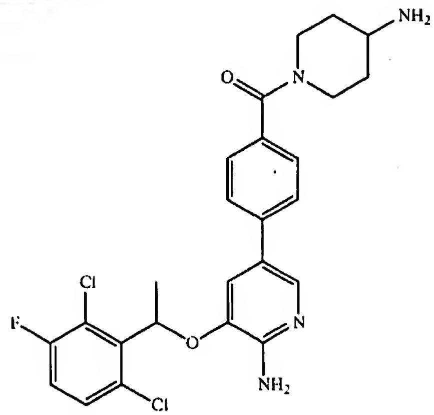
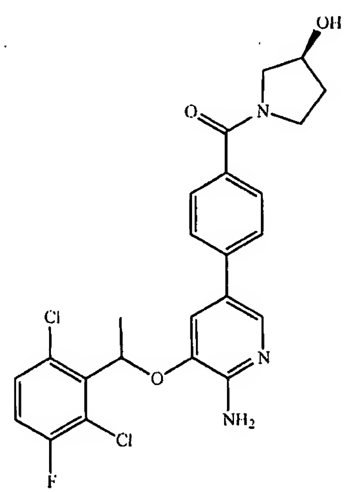
I-305		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-amino-piperidin-1-yl)-methanone	0.18	4 as in Example I-291		504 [M + 1]
I-306		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone	0.024	4 as in Example I-291	(300 MHz, CD3OD) δ 7.78(d, 1H), 7.47(m, 3H), 7.37(m, 3H), 6.92(d, 1H), 6.07(q, 1H), 5.88(s, 2H), 4.82(dd, 1H), 4.15(d, 1H), 3.53 (m, 2H), 3.42(m, 1H), 3.15(m, 1H), 2.43(m, 1H), 1.85(m, 1H), 1.75(d, 3H).	491 [M + 1]

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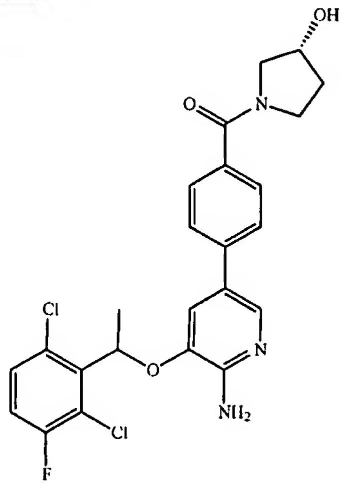
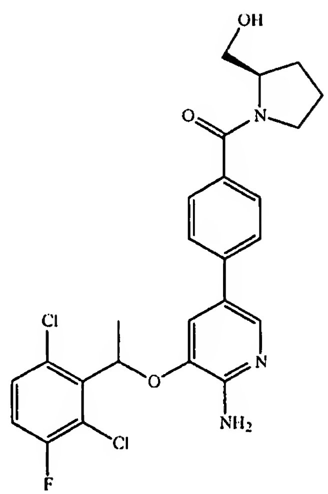
I-307		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone	0.022	4 as in Example I-291	(300 MHz, CD3OD) δ 7.80(d, 1H), 7.47(m, 3H), 7.37(m, 3H), 6.92(d, 1H), 6.07(q, 1H), 5.89(s, 2H), 4.82(dd, 1H), 4.15(d, 1H), 3.53 (m, 2H), 3.42(m, 1H), 3.15(m, 1H), 2.43(m, 1H), 1.85(m, 1H), 1.75(d, 3H).	491 [M + 1]
I-308		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-methanone	0.033	4 as in Example I-291	(300 MHz, CD3OD) δ 7.80(d, 1H), 7.47(m, 3H), 7.37(m, 3H), 6.92(d, 1H), 6.07(q, 1H), 5.89(s, 2H), 4.70(m, 1H), 4.05(m, 1H), 3.5(m, 2H), 3.32(m, 1H), 2.43(m, 1H), 1.85(m, 3H), 1.75(d, 3H), 1.15(m, 1H).	505 [M + 1]

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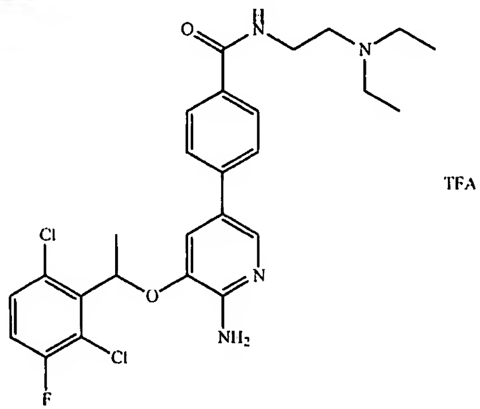
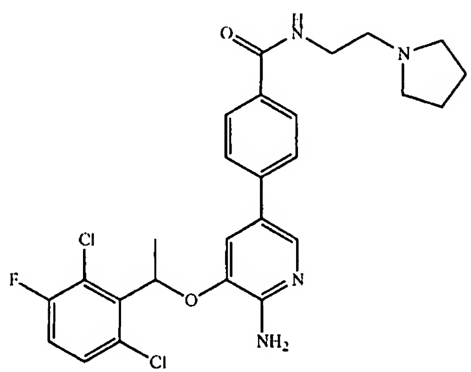
I-309		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-diethylamino-ethyl)-benzamide	0.04	4 as in Example I-291	(300 MHz, CDCl3) δ 9.55 (bm, 1H), 8.80 (t, 1H), 7.95(s, 1H), 7.58(d, 2H), 7.55(m, 3H), 7.45(t, 1H), 7.09(d, 1H), 6.23(q, 1H), 3.60(q, 2H), 3.22 (m, 5H, 3.09(m, 1H), 1.85(d, 3H), 1.22(dd, 6).	516 [M + 1]
I-310		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.12	4 as in Example I-291	(300 MHz, CDCl3) δ 8.25 (bm, 1H), 7.90 (d, 1H), 7.82(s, 2H), 7.34(d, 2H), 7.25(m, 1H), 7.04(t, 1H), 6.96(s, 1H), 6.09(q, 1H), 4.97(s, 2H), 3.82 (m, 2H), 3.15(m, 6H), 2.00(m, 4H), 1.85(d, 3H).	518 [M + 1]

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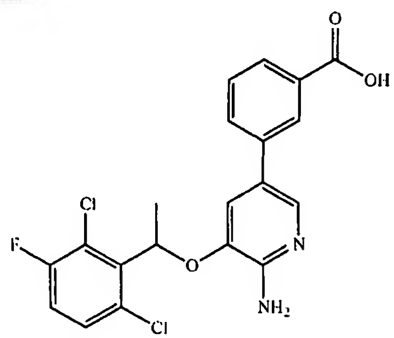
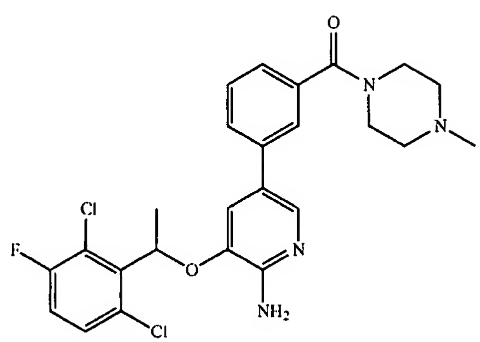
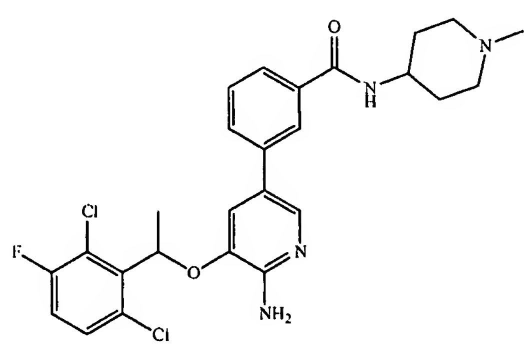
I-311		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		3 as in Example 211		420 [M − 1]
I-312		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.062	4	(300 MHz, CDCl3) δ 7.86(s, 1H), 7.41 (m, 3H), 7.30(m, 3H), 7.07(t, 1H), 6.99(s, 1H), 6.12 (q, 1H), 4.99(s, 2H), 3.89(m, 2H), 3.50(m, 2H), 2.54(m, 2H), 2.40(m, 2H), 2.35(s, 3H), 1.87(d, 3H).	503 [M + 1]
I-313		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl) benzamide	0.069	4 as in Example I-312	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.76 (s, 1H), 7.67(d, 1H), 7.49(d, 1H), 7.42(t, 1H), 7.31(dd, 1H), 7.05 (t, 1H), 7.01(s, 1H), 6.28 (bd, 1H), 6.12 (q, 1H), 4.99(s, 2H), 4.08(m, 1H), 3.04(m, 2H), 2.42(s, 3H), 2.32(m, 2H), 2.10(m, 2H), 1.87(d, 3H), 1.80(m, 2H).	517 [M + 1]

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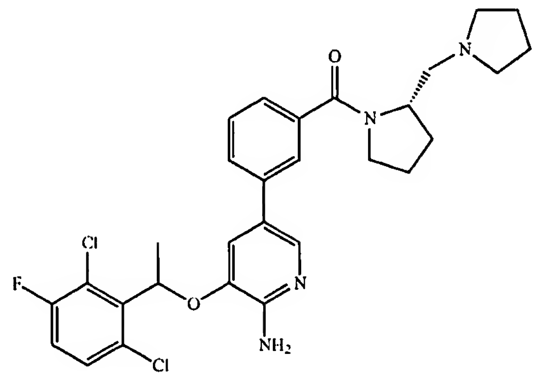
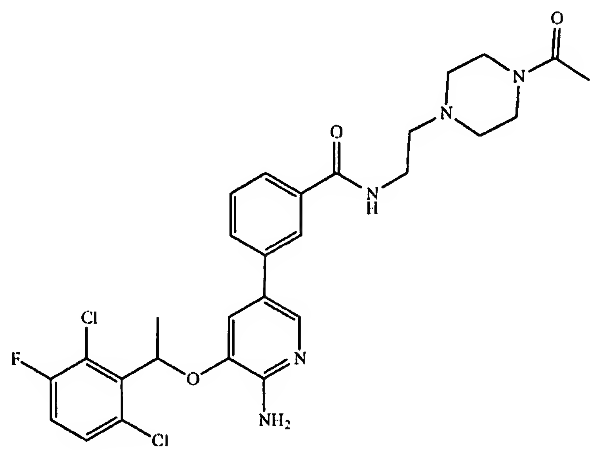
I-314		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.06	4 as in Example I-312	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.40(m, 4H), 7.29(dd, 1H), 7.05(t, 1H), 7.00(s, 1H), 6.12 (q, 1H), 4.92 (s, 2H), 3.50(m, 2H), 3.74(m, 4H), 1.86(d, 3H), 1.57–2.18(m, 11H),	559 [M + 1]
I-315		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide	0.069	4 as in Example I-312	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.83 (s, 1H), 7.65(d, 1H), 7.46(m, 2H), 7.32(dd, 1H), 7.06(t, 1H), 7.03 (s, 1H), 6.95 (bt, 1H), 6.12 (q, 1H), 5.08(s, 2H), 3.66(m, 4H), 3.50 (m, 2H), 2.73(m, 2H), 2.52(m, 4H), 2.09(s, 3H), 1.87(d, 3H).	576 [M + 1]

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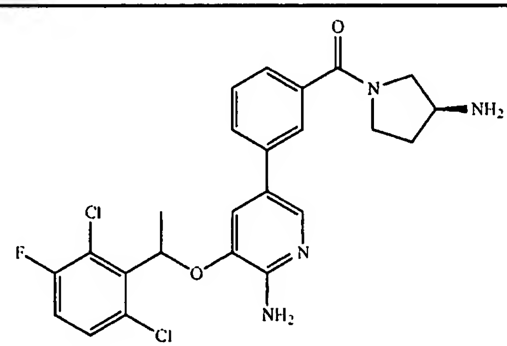
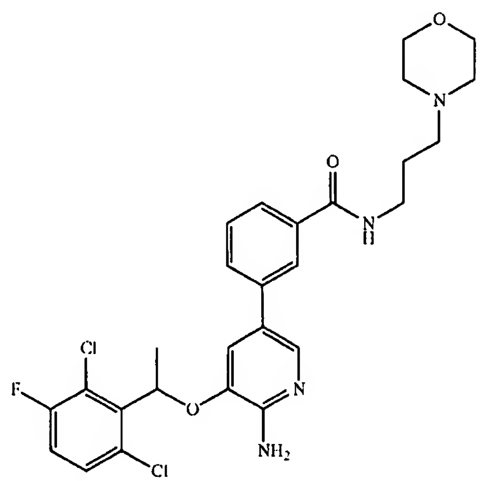
I-316		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone	0.048	4 as in Example I-312	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.38(m, 4H), 7.28(m, 1H), 7.06(t, 1H), 6.98(s, 1H), 6.12 (q, 1H), 5.05(s, 2H), 3.82(m, 2H), 3.72 (m, 2H), 2.10(m, 1H), 1.86(d, 3H), 1.84(m, 2H).	491 [M + 1]
I-317		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide	0.059	4 as in Example I-312	(300 MHz, CDCl3) δ 7.91(s, 1H), 7.87(s, 1H), 7.85(d, 1H), 7.50(m, 2H), 7.31(dd, 1H), 7.04(m, 2H), 6.13(q, 1H), 4.93(s, 2H), 3.64(m, 6H), 2.50(m, 6H), 1.87(d, 3H), 1.81(m, 2H), 1.81(m, 2H).	549 [M + 1]

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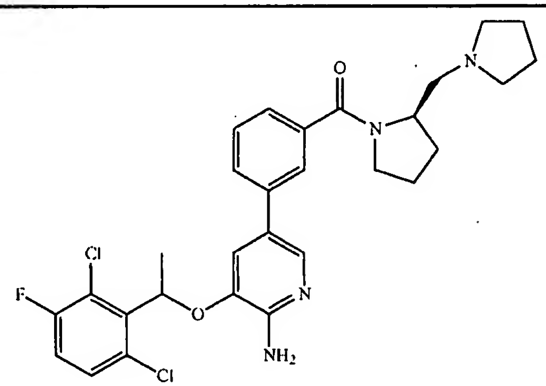
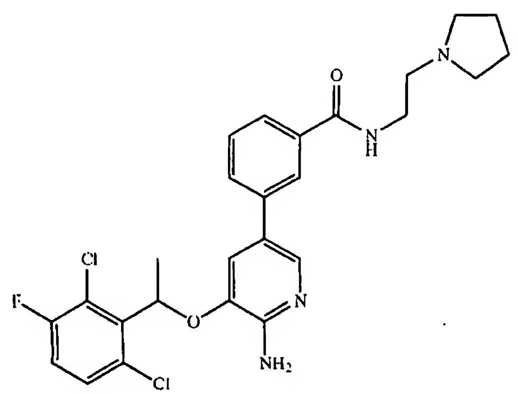
I-318		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.13	4 as in Example I-312	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.40(m, 4H), 7.29(dd, 1H), 7.05(t, 1H), 7.00(s, 1H), 6.12 (q, 1H), 4.92(s, 2H), 3.50(m, 2H), 3.74(m, 4H), 1.86(d, 3H), 1.57–2.18(m, 11H).	558 [M + 1]
I-319		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.1	4 as in Example I-312	(300 MHz, CDCl3) δ 7.86(s, 1H), 7.82(s, 1H), 7.73(d, 1H), 7.46(m, 4H), 7.22 (t, 1H), 7.04(s, 1H), 6.95 (bt, 1H), 6.22(q, 1H), 4.82(s, 2H), 360 (m, 2H), 2.82(m, 2H), 2.70(m, 4H), 1.87 (d, 3H), 1.82(m, 2H).	518 [M + 1]

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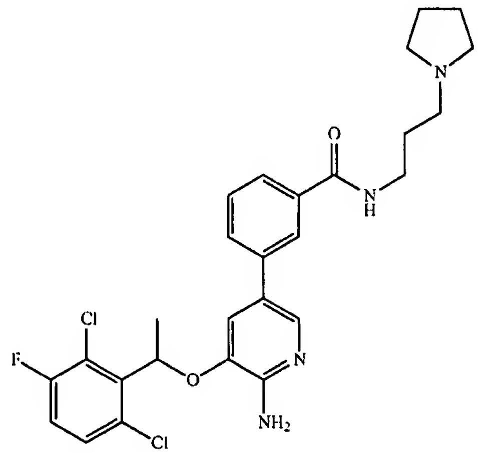
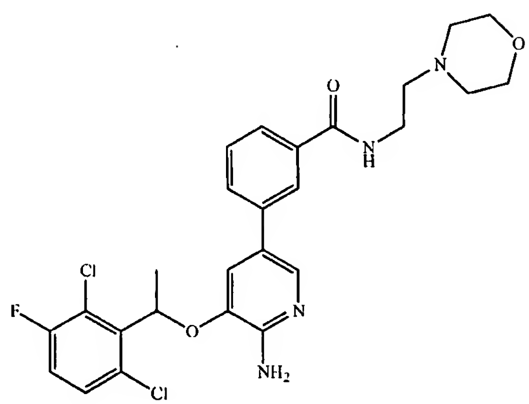
I-320		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.13	4 as in Example I-312	(300 MHz, CDCl3) δ 8.66 (bt, 1H), 7.90 (s, 1H), 7.85(s, 1H), 7.61(d, 1H), 7.42(m, 2H), 7.31(dd, 1H), 7.05(m, 2H), 6.14(q, 1H), 4.88(s, 2H), 3.65(m, 2H), 2.71(m, 2H), 2.56(m, 4H), 1.87(d, 3H), 1.80 (m, 2H), 1.71(m, 4H).	531 [M + 1]
I-321		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.18	4 as in Example I-312	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.84 (s, 1H), 7.66(d, 1H), 7.46(m, 2H), 7.32(dd, 1H), 7.05(m, 2H), 6.88 (bt, 1H), 6.14(q, 1H), 5.04(s, 2H), 3.82(m, 4H), 3.66(m, 2H), 2.72(t, 2H), 2.60(m, 4H), 1.88 (d, 3H).	535 [M + 1]

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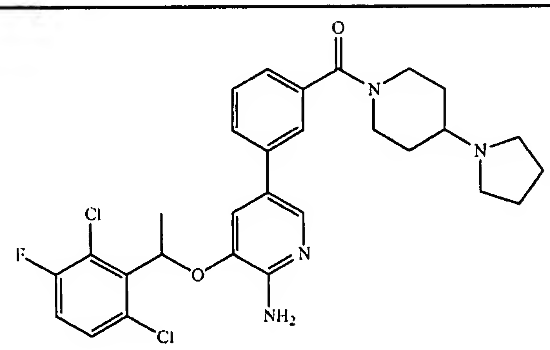
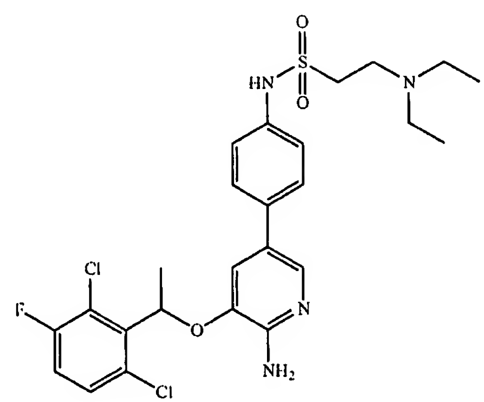
I-322		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.071	4 as in Example I-312	(300 MHz, CDCl3) δ 7.86(s, 1H), 7.41 (m, 3H), 7.30(m, 3H), 7.07(t, 1H), 6.99(s, 1H), 6.12 (q, 1H), 4.95(s, 2H), 4.70(m, 1H), 3.82(m, 1H), (m, 1H), 2.98(m, 1H), 2.65(m, 4H), 2.28(m, 1H), 1.02(m, 1H), 1.81 (m, 5H), 1.55(m, 2H).	559 [M + 1]
I-323		2-Diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.08	9	(300 MHz, CDCl3) δ 7.83(s, 1H), 7.32 (m, 4H), 7.21(d, 2H), 7.06(t, 1H), 6.96(s, 1H), 5.96(q, 1H), 4.81(s, 2H), 3.22(m, 2H), 3.02(m, 2H), 2.62(m, 4H), 1.84(d, 3H), 1.08 (t, 6H),	571 [M + 1]

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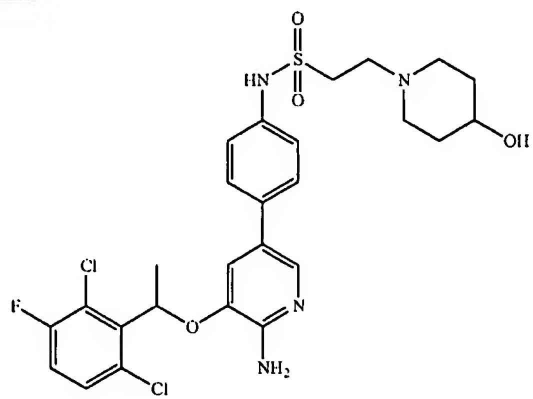
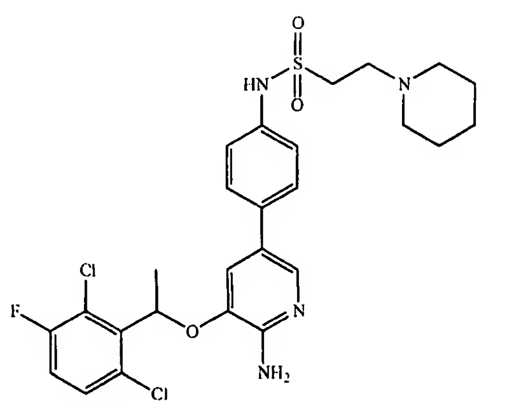
I-324		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy[-pyridin-3-yl}-phenyl)-amide	0.059	9 as in Example I-297	(300 MHz, CDCl3) δ 7.81(s, 1H), 7.31 (m, 3H), 7.25(m, 3H), 7.07(t, 1H), 6.96(s, 1H), 6.11(q, 1H), 4.95(s, 2H), 3.76(m, 1H), 3.25(t, 2H), 2.92(t, 2H), 2.79(m, 2H), 2.25 (m, 2H), 1.93(m, 2H), 1.86(d, 3H), 1.62(m, 2H).	583 [M + 1]
I-325		2-Piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy[-pyridin-3-yl}-phenyl)-amide	0.089	9 as in Example I-297	(300 MHz, CDCl3) δ 7.84(s, 1H), 7.32 (m, 4H), 7.21(d, 2H), 7.06(dd, 1H), 6.96(s, 1H), 6.11(q, 1H), 4.88(s, 2H), 3.24(t, 2H), 2.89(t, 2H), 2.48(m, 4H), 1.86(d, 3H), 1.62(m, 4H), 1.49(m, 2H),	558 [M + 1]

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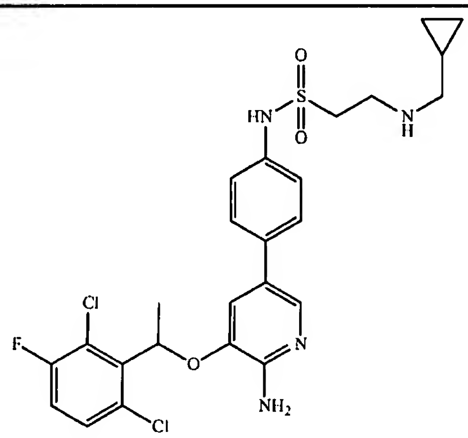
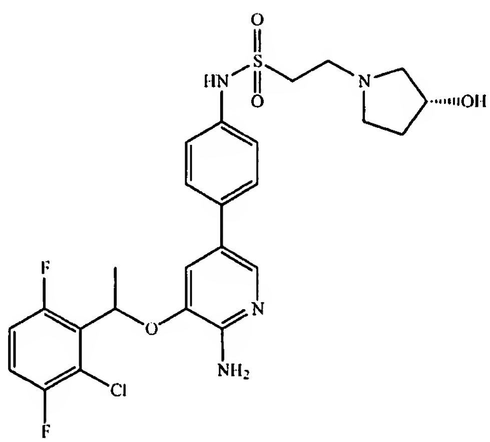
I-326		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.075	9 as in Example I-297	(300 MHz, CDCl3) δ 7.83(s, 1H), 7.28 (m, 6H), 7.06(dd, 1H), 6.96(s, 1H), 6.11(q, 1H), 4.91(s, 2H), 3.22(m, 4H), 2.50(d, 2H), 1.86(d, 3H), 0.84(m, 2H), 0.52(m, 2H), 0.15(m, 1H).	517 [M + 1]
I-327		2-((R)-3-Hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy[-pyridin-3-yl}-phenyl)-amide	0.093	9 as in Example I-286	(300 MHz, CDCl3) δ 7.83(s, 1H), 7.32 (m, 5H), 7.05(m, 3H), 5.95(q, 1H), 4.84(s, 2H), 4.43(m, 1H), 3.25(m, 2H), 3.02(m, 3H), 2.84(m, 1H), 2.53(m, 1H), 2.30(m, 1H), 2.22(m, 1H), 1.84(d, 3H), 1.81(m, 1H).	553 [M + 1]

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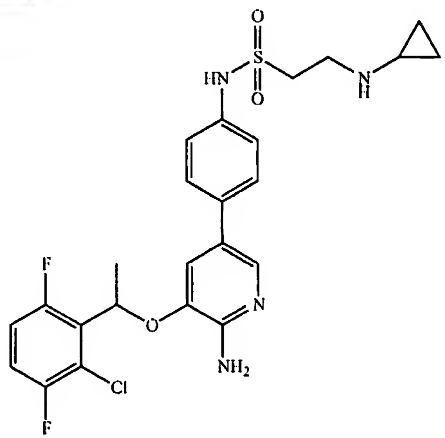
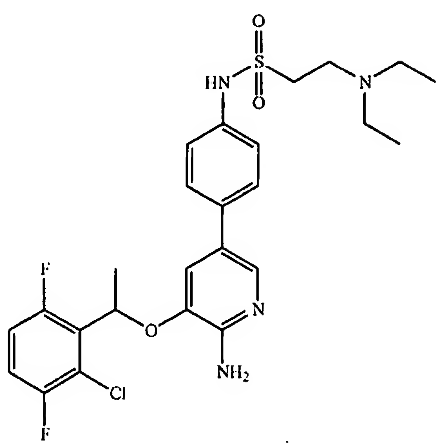
I-328		2-Cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.16	9 as in Example I-286	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.38 (d, 2H), 7.24(m, 2H), 7.18(m, 3H), 5.95(q, 1H), 4.89(s, 2H), 3.22(m, 4H), 2.14(m, 1H), 1.85(d, 3H), 0.50(m, 2H), 0.38(m, 2H).	523 [M + 1]
I-329		2-Diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.095	9 as in Example I-286	(300 MHz, CDCl3) δ 7.84(s, 1H), 7.34 (d, 2H), 7.23(m, 3H), 7.02(m, 3H), 5.96(q, 1H), 4.81(s, 2H), 3.22(m, 2H), 3.02(m, 2H), 2.62(m, 4H), 1.84(d, 3H), 1.08(t, 6H).	539 [M + 1]

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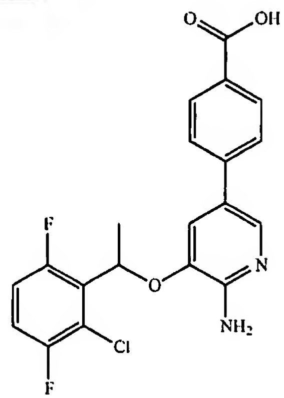
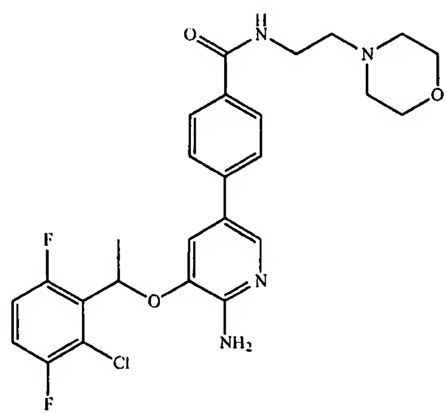
I-330		4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		3 as in Example 211		405 [M + 1]
I-331		4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.13	4	(300 MHz, CDCl3) δ 7.91(s, 1H), 7.80 (d, 2H), 7.46(d, 2H), 7.05(m, 3H), 6.87(m, 1H), 5.97(q, 1H), 4.97(s, 2H), 3.75(m, 4H), 3.58(m, 2H), 2.60(m, 6H), 1.84(m, 3H).	517 [M + 1]

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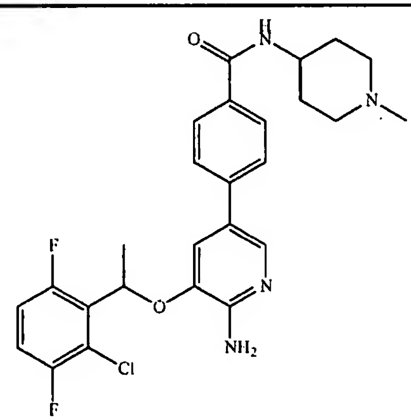
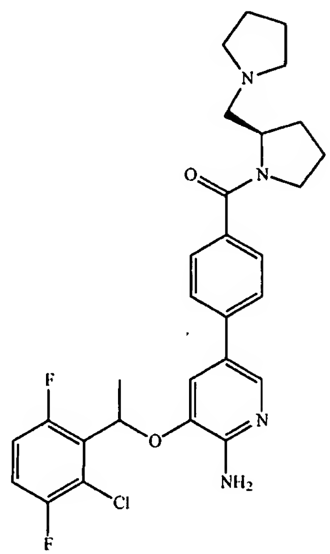
I-332		4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.079	4 as in Example I-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.78 (d, 2H), 7.45(d, 2H), 7.05(m, 4H), 5.98(q, 1H), 4.90(s, 2H), 4.00(m, 1H), 2.88(m, 2H), 2.32(s, 3H), 2.18(m, 2H), 2.08(m, 2H), 1.84 (d, 3H), 1.57(m, 2H).	501 [M + 1]
I-333		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.067	4 as in Example I-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.54(m, 2H), 7.42(d, 2H), 7.05(m, 3H), 5.98(q, 1H), 4.86(s, 2H), 3.50(m, 2H), 3.74(m, 4H), 1.84(d, 3H), 1.57–2.18(m, 11H)	541 [M + 1]

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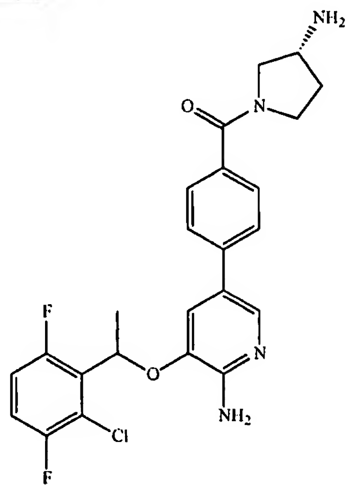
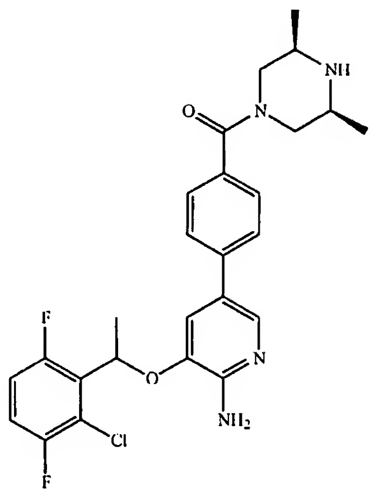
1-334		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.089	4 as in Example 1-331	(300 MHz, CDCl3) δ 7.68(m, 5H), 7.25(m, 3H), 6.27(m, 1H), 4.88(s, 2H), 3.75(m, 5H), 3.31(m, 2H), 2.44(m, 18), 2.17(m, 1H), 1.93(m, 3H).	473 [M + 1]
1-335		(4-{6 Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.09	4 as in Example 1-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.42(m, 4H), 7.05(m, 3H), 5.97(q, 1H), 4.86(s, 2H), 4.62(m, 1H), 3.65(m, 1H), 2.88(m, 2H), 2.68(m, 1H), 2.41(m, 1H), 1.84 (d, 3H), 1.64(m, 1H), 1.05(m, 6H).	501 [M + 1]

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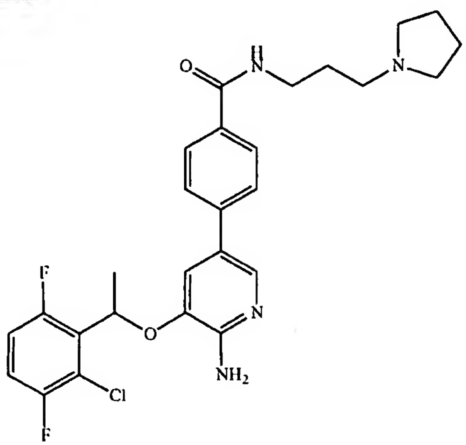
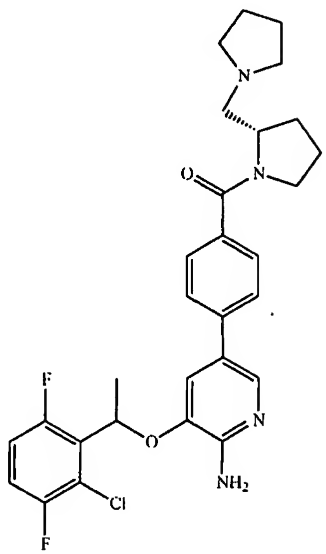
I-336 	4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.09	4 as in Example I-331	(300 MHz, CDCl3) δ 9.00(s, 1H), 7.92(s, 1H), 7.83(d, 2H), 7.42(d, 2H), 7.06(m, 2H), 7.01(m, 1H), 5.96(q, 1H), 4.89(s, 2H), 3.60(m, 2H), 2.75(m, 2H), 2.62(m, 4H), 1.85(m, 7H).	515 [M + 1]
I-337 	(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.09	4 as in Example I-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.53(m, 2H), 7.43(d, 2H), 7.05(m, 3H), 5.98(q, 1H), 4.88(s, 2H), 4.45(m, 1H), 3.58(m, 2H), 3.00(m, 4H), 1.84(d, 3H), 1.70–2.18(m, 10H)	541 [M + 1]

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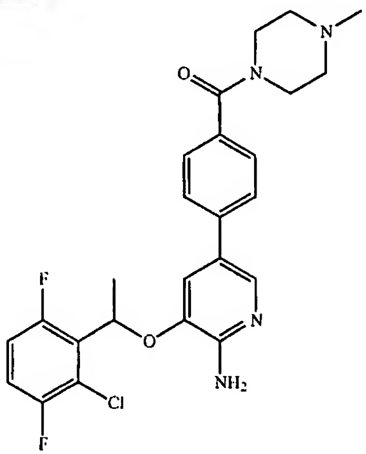
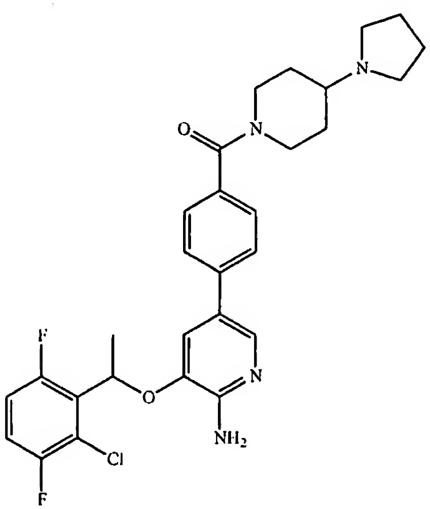
I-338		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.077	4 as in Example I-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.44(m, 4H), 7.07(m, 3H), 5.95 (q, 1H), 4.87(s, 2H), 3.60(m, 4H), 2.43(m, 4H), 2.33(s, 3H), 1.84(d, 3H).	487 [M + 1]
I-399		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.062	4 as in Example I-331	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.42(m, 4H), 7.02(m, 3H), 6.00 (q, 1H), 4.87(s, 2H), 4.64(m, 1H), 3.85(m, 1H), 2.99(m, 2H), 2.67(m, 4H), 2.38(m, 1H), 1.90(m, 9H), 1.62(m, 2H).	541 [M + 1]

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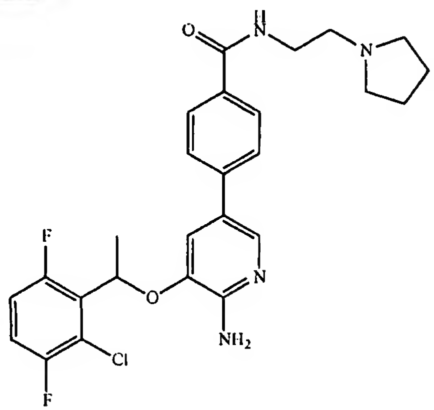
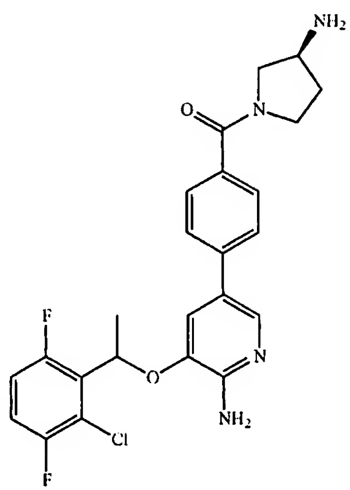
I-340		4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.086	4 as in Example I-331	(300 MHz, CDCl3) δ 7.91(s, 1H), 7.86(d, 2H), 7.45(d, 2H), 7.10 (m, 3H), 7.01(m, 1H), 5.98(q, 1H), 4.90(s, 2H), 3.60(m, 2H), 2.80(m, 2H), 2.68(m, 4H), 1.85(m, 7H).	501 [M + 1]
I-341		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone	0.075	4 as in Example I-331	(300 MHz, CDCl3) δ 7.76(s, 1H), 7.67(m, 2H), 7.59(d, 2H), 7.42 (s, 1H), 7.32(m, 1H), 7.20(m, 1H), 6.27(m, 1H), 4.86(s, 2H), 3.75(m, 5H), 3.31(m, 2H), 2.44(m, 1H), 2.14 (m, 1H), 1.95(m, 3H).	473 [M + 1]

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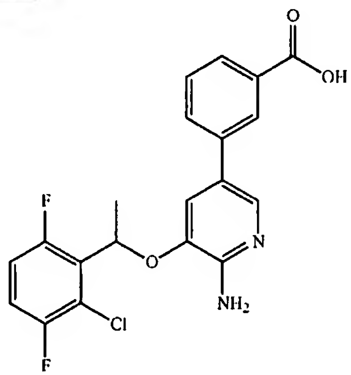
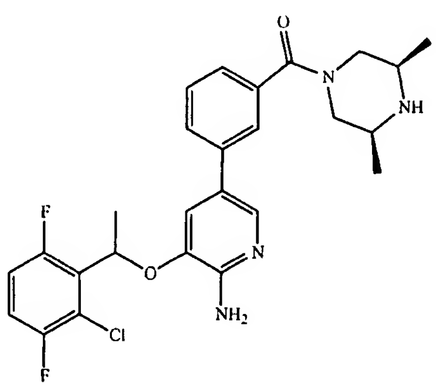
I-342		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		as in Example 211		405 [M + 1]
I-343		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.16	4	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.43(m, 2H), 7.30(m, 2H), 7.10 (m, 2H), 6.95(m, 1H), 5.97(q, 1H), 4.87(s, 2H), 4.65(m, 1H), 3.60(m, 1H), 2.72(m, 3H), 2.41(m, 1H), 2.01 (s, 1H), 1.84(d, 3H), 1.17 (m, 3H), 0.98(m, 3H).	501 [M + 1]

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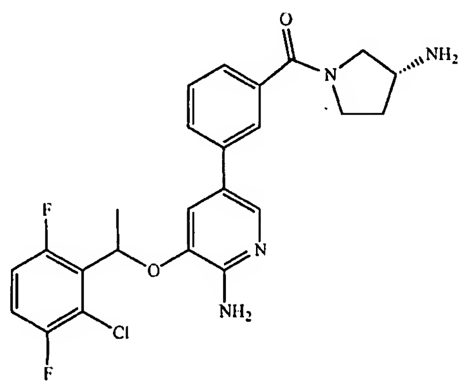
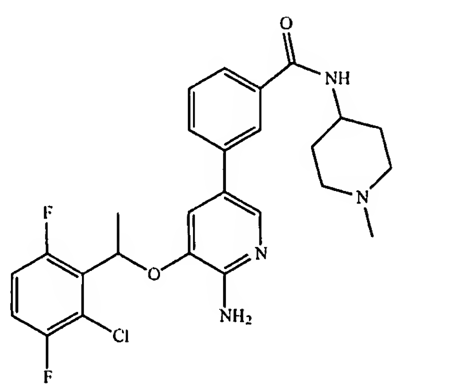
I-344		(3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.12	4 as in Example 343	(300 MHz, CDCl3) δ 7.65(m, 5H), 7.42(s, 1H), 7.32(m, 1H), 7.20 (m, 1H), 6.27(m, 1H), 4.85(s, 2H), 3.75(m, 5H), 3.31(m, 2H), 2.44(m, 1H), 2.16(m, 1H), 1.93(m, 3H).	473 [M + 1]
I-345		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.2	4 as in Example 343	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.78(s, 1H), 7.67(d, 1H), 7.45 (m, 2H), 7.00(m, 3H), 6.15 (bd, 1H), 5.98(q, 1H), 4.08(m, 1H), 2.97 (m, 2H), 2.38(s, 3H), 2.27(m, 2H), 2.10(m, 2H), 1.84(d, 3H), 1.74(m, 2H).	501 [M + 1]

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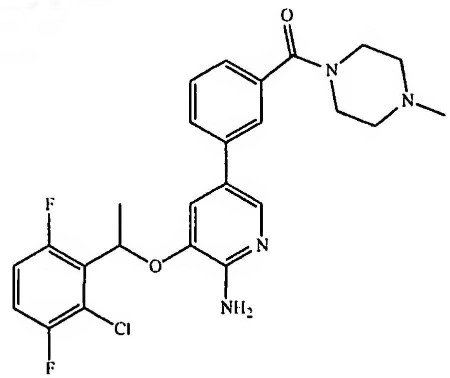
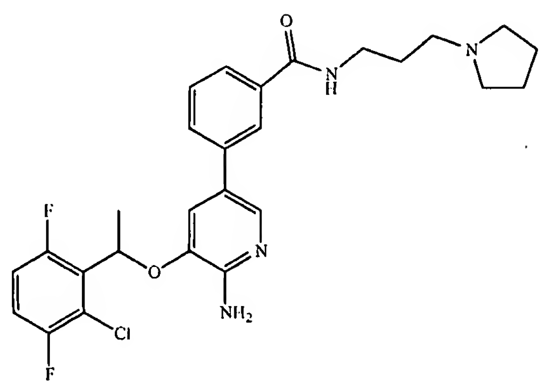
I-346		(3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.19	4 as in Example 343	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.42(m, 3H), 7.30(m, 2H), 7.09 (m, 2H), 7.00(m, 1H), 5.95(q, 1H), 4.87(s, 2H), 3.83(m, 2H), 3.47 (m, 2H), 2.51(m, 2H), 2.33(m, 5H), 1.84(d, 3H).	487 [M + 1]
I-347		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.21	4 as in Example 343	(300 MHz, CDCl3) δ 8.69(s, 1H), 7.91(m, 2H), 7.65(d, 1H), 7.42 (m, 2H), 7.00(m, 3H), 5.99(q, 1H), 4.85(s, 2H), 3.60(m, 2H), 2.76 (m, 2H), 2.63(m, 4H), 1.84(d, 3H), 1.77(m, 6H).	515 [M + 1]

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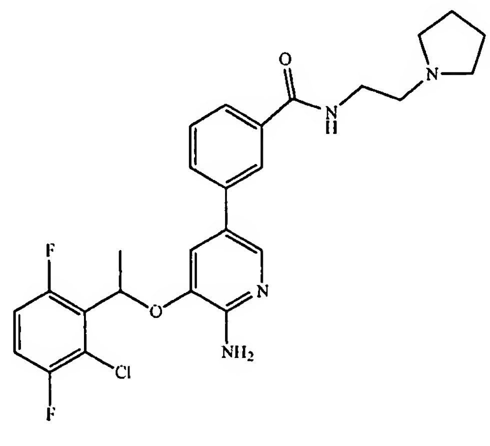
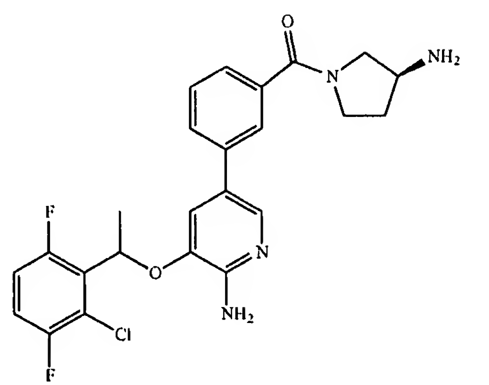
I-348		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.2	4 as in Example 343	(300 MHz, CDCl3) δ 7.91(s, 1H), 7.86(s, 1H), 7.70(d, 1H), 7.50 (m, 2H), 7.00(m, 4H), 5.99(q, 1H), 4.86(s, 2H), 3.60(m, 2H), 2.78 (m, 2H), 2.63(m, 4H), 1.85(m, 7H).	501 [M + 1]
I-349		(3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone	0.13	4 as in Example 343	(300 MHz, CDCl3) δ 7.70(m, 5H), 7.42(s, 1H), 7.28(m, 1H), 7.20 (m, 1H), 6.27(m, 1H), 4.85(s, 2H), 3.75(m, 5H), 3.31(m, 2H), 2.66 (m, 1H), 2.44(m, 1H), 1.93(m, 3H).	473 [M + 1]

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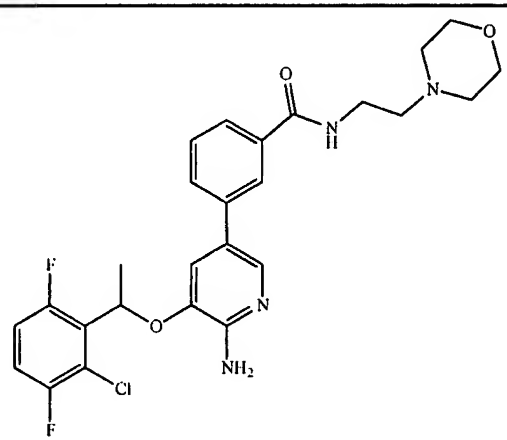
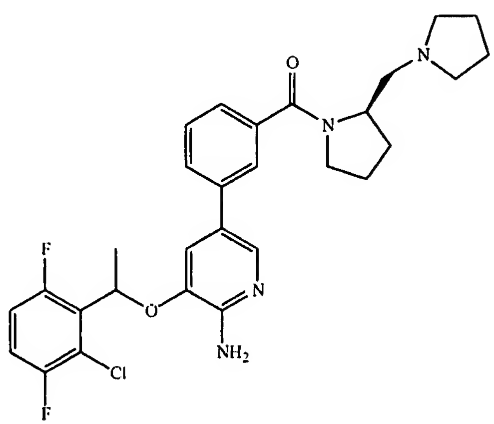
I-350		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.39	4 as in Example 343	(300 MHz, CDCl3) δ 7.91(s, 1H), 7.84(s, 1H), 7.65(d, 1H), 7.46 (m, 2H), 7.05(m, 3H), 6.83 (bs, 1H), 5.97(q, 1H), 4.91(s, 2H), 3.74(m, 4H), 3.58(m, 2H), 2.63(m, 2H), 2.52(m, 4H), 1.84(m, 3H).	517 [M + 1]
I-351		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.23	4 as in Example 343	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.45(m, 4H), 7.05(m, 3H), 5.98 (q, 1H), 4.86(s, 2H), 4.45 (m, 1H), 3.64(m, 1H), 3.44(m, 1H), 2.64(m, 4H) 1.83(d, 3H), 1.70–2.18(m, 10H)	541 [M + 1]

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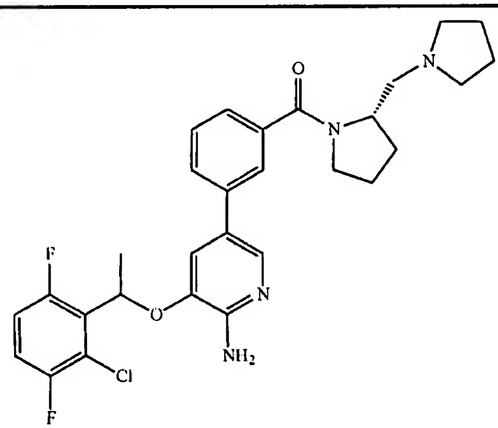
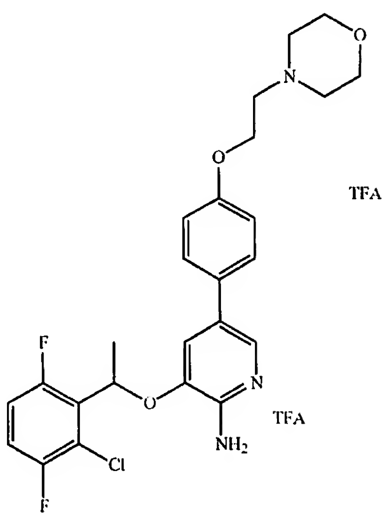
I-352		3-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.15	4 as in Example 343	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.45(m, 4H), 7.09(m, 3H), 5.98 (q, 1H), 4.86(s, 2H), 4.45 (m, 1H), 3.45(m, 2H), 2.75(m, 4H), 1.84(d, 3H), 1.70-2.18(m, 10H)	541 [M + 1]
I-353		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.23	3 as in Example I-2		

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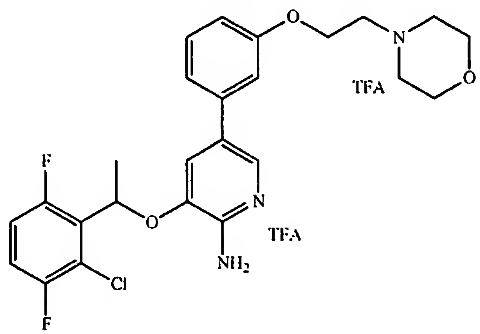
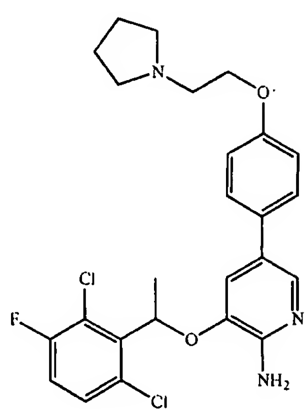
I-354		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.22	3 as in Example I-2		
I-355		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.068	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.74(d, J=2.0 Hz, 1H), 7.53(m, 1H), 7.44(m, 2H), 7.32(d, J=9.0 Hz, 2H), 7.00(d, J=8.6 Hz, 2H), 6.88 (d, J=1.6 Hz, 1H), 6.11(m, 1H), 5.79(s, 2H), 4.30(m, 2H), 3.5(m, 6H), 1.90(m, 4H), 1.807(d, J=6.7 Hz, 3H).	491 [M + 1]

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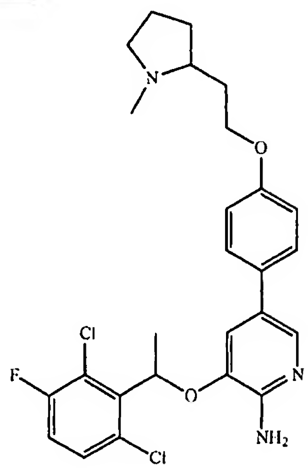
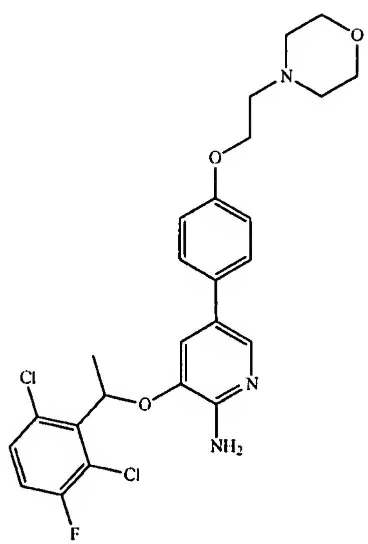
I-356		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-{4-[2-1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-pyridin-2-ylamine	0.079	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.73(s, 1H), 7.54 (m, 1H), 7.44(m, 2H), 7.284(d, J=8.2 Hz, 2H), 6.95(d, J=8.6 Hz, 2H), 6.88(s, 1H, pyridine-H), 6.10(m, 1H), 5.78(s, 2H), 4.7(m, 1H), 3.3(m, 2H), 3.1(m, 2H), 2.77(s, 3H), 2.3(m, 6H), 1.81(d, J=6.2 Hz, 3H).	504 [M + 1]
I-357		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.13	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.72(d, 1H), 7.53 (m, 1H), 7.44(m, 1H), 7.33(m, 2H), 7.03(m, 3H), 6.23(q, 1H), 4.35(m, 2H), 3.95(m, 1H), 3.0-3.8(m, 9H), 1.851(d, 3H).	506 [M + 1]

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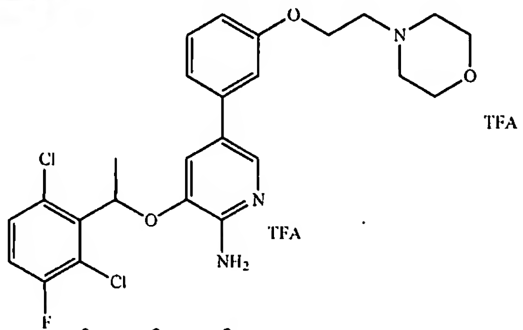
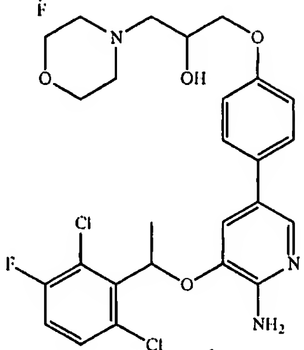
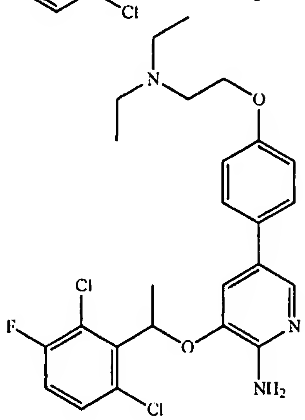
I-358		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine	0.22	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.82(d, 1H), 7.53 (q, 1H), 7.46(t, 1H), 7.33(t, 1H), 7.03(m, 3H), 6.95(dd, 1H), 6.24(q, 1H), 4.38(m, 2H), 3.95(m, 2H), 3.75(m, 2H), 3.61(m, 2H), 3.5(m, 2H), 3.25(m, 2H), 1.851(d, 3H).	506 [M + 1]
I-359		1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-3-morpholin-4-yl-propan-2-ol	0.045	3	(400 MHz, DMSO-d6): d 7.73(d, J=1.6 Hz, 1H), 7.56(m, 1H), 7.44(t, J=8.6 Hz, 1H), 7.28(d, J=6.7 Hz, 2H), 6.94(d, J=8.6 Hz, 2H), 6.88 (d, J=2.0 Hz, 1H), 6.11(m, 1H), 5.75(s, 2H), 4.88 (d, J=2.0 Hz, 1H), 3.96(m, 3H), 3.57 (t, J=4.3 Hz, 4H), 2.42 [m, 6H), 1.81(d, J=6.7 Hz, 3H).	536 [M + 1]
I-360		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diethylamino-ethoxy)-phenyl]-pyridin-2-ylamine	0.033	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.73(d, J=1.6 Hz, 1H), 7.56(m, 1H), 7.44(t, J=8.6 Hz, 1H), 7.28(d, J=8.6 Hz, 2H), 6.92(d, J=8.6 Hz, 2H), 6.88 (d, J=1.6 Hz, 1H), 6.11(m, 1H), 5.75(s, 2H), 4.02(t, J=6.2 Hz, 2H), 2.756(m, 2H), 2.55 (m, 4H), 1.81(d, J=6.7 Hz, 3H), 0.99(t, J=7.0 Hz, 6H).	494 [M + 1]

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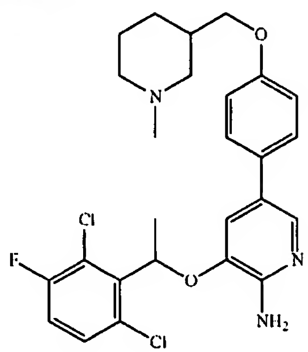
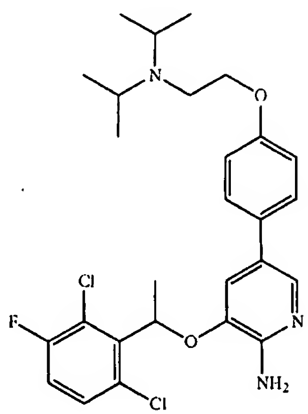
I-361		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-3-ylmethoxy)-phenyl]-pyridin-2-ylamine	0.043	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.73(d, J=2.0 Hz, 1H), 7.53(m, 1H), 7.44(t, J=8.6 Hz, 1H), 7.27(d, J=6.7 Hz, 2H), 6.92(d, J=8.6 Hz, 2H), 6.87(d, J=1.6 Hz, 1H), 6.10(m, 1H), 5.75(s, 2H), 3.831(m, 2H), 2.81(m, 1H), 2.62(s, 1H), 2.153(s, 3H), 1.95(m, 3H), 1.81(d, J=6.7 Hz, 3H), 1.72(m, 4H).	504 [M + 1]
I-362		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diisopropylamino)-ethoxy)-phenyl]-pyridin-2-ylamine	0.052	3 as in Example I-2	(400 MHz, DMSO-d6): d 7.73(d, J=2.0 Hz, 1H), 7.53(m, 1H), 7.44(t, J=8.6 Hz, 1H), 7.27(m, 2H), 6.91(m, 2H), 6.88(d, J=2.0 Hz, 1H), 6.11(m, 1H), 5.74 (s, 2H), 3.88(t, J=6.7 Hz, 2H), 3.02(m, 2H), 2.76(t, 3 =6.7 Hz, 2H), 1.81(d, J= 6.7 Hz, 3H), 0.986(m, 12H).	520 [M + 1]

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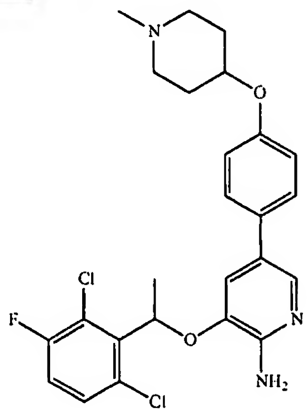
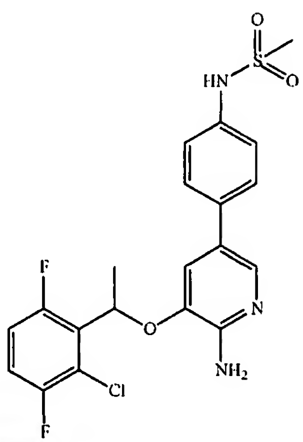
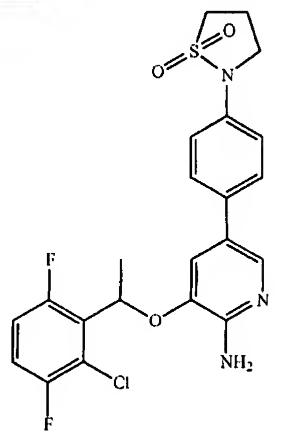
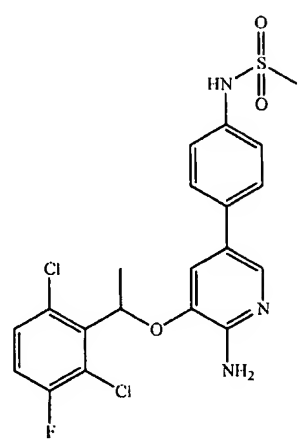
I-363		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-pyridin-2-ylamine	0.052	3	(400 MHz, DMSO-d6): d 7.66(d, J=1.6 Hz, 1H), 7.49(m, 1H), 7.377(t, J=8.2 Hz, 1H), 7.20(m, 2H), 6.87(m, 2H), 6.81(d, J=1.6 Hz, 1H), 6.04 (m, 1H), 5.68(s, 2H), 4.30(m, 1H), 2.55(m, 2H), 2.12 (m, 5H), 1.84(m, 2H), 1.74(d, J=6.7 Hz, 3H), 1.57(m, 2H).	490 [M + 1]
I-364		N-(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide	0.1	3 as in Example I-135		454 [M + 1]

I-365		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(1,1-dioxo-1lambda*6*-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine	0.14	3 as in Example I-240		478 [M + 1]
I-366		N-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide	0.076	3 as in Example I-135	(300 MHz, CDCl3) δ 9.75(s, 1H), 7.88(d, 1H), 7.55(q, 1H), 7.45(t, 1H), 7.35(d, 2H), 7.18(d, 2H), 6.9(d, 1H), 6.10(q, 1H), 5.85(s, 2H), 2.99(s, 3H), 1.80(d, 3H).	470 [M + 1]

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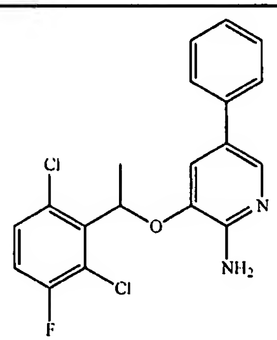
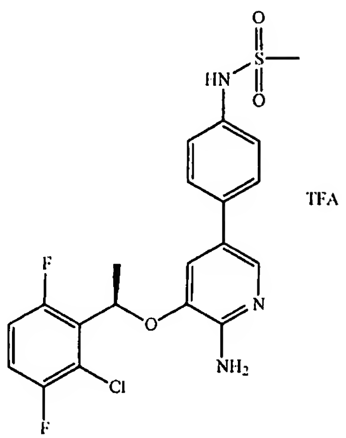
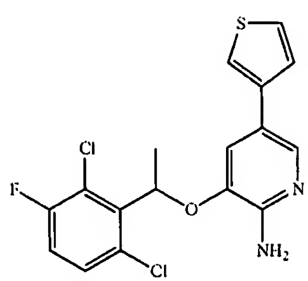
I-367		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-phenyl-pyridin-2-ylamine	0.5	3	(300 MHz, CDCl3) δ 7.80(d, 1H), 7.55(q, 1H), 7.45(t, 1H), 7.35(dd, 4H), 7.25(m, 1H), 6.95(d, 1H), 6.12 (q, 1H), 5.85(s, 2H), 1.80(d, 3H).	377 [M + 1]
I-368		N-(4-{6-Amino-5-[(R)-1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide	0.066	3 as in Example I-135	(300 MHz, CDCl3) δ 9.80(s, 1H), 7.70(d, 1H), 7.43(m, 3H), 7.30(ddd, 1H), 7.25(d, 1H), 7.18(m, 2H), 6.10(q, 1H), 2.95(s, 3H), 1.75(d, 3H).	454 [M + 1]
I-369		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-thiophen-3-yl-pyridin-2-ylamine	0.055	3		383 [M + 1]

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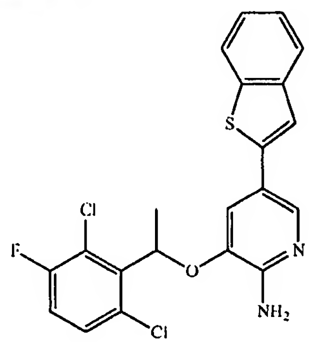
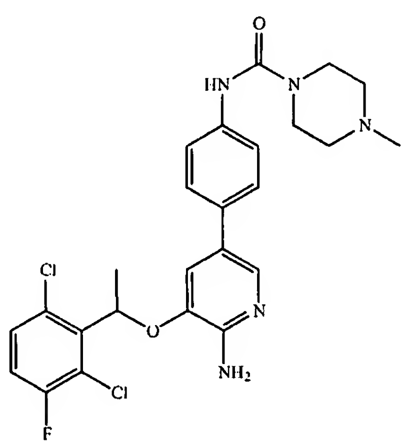
I-370		5-Benzo[b]thiophen-2-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine	1.95	3		433 [M + 1]
I-371		4-Methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.057	10	(300 MHz, CDCl3) δ 7.71(s, 1H), 7.40(d, 2H), 7.32–7.23(m, 3H), 7.06 (t, 1H), 6.99(s, 1H), 6.77(bs, 1H), 6.11(q, 1H), 5.62(s, 2H), 3.60 (m, 4H), 2.57(m, 4H), 2.40(s, 3H), 1.87(d, 3H).	518 [M + 1]

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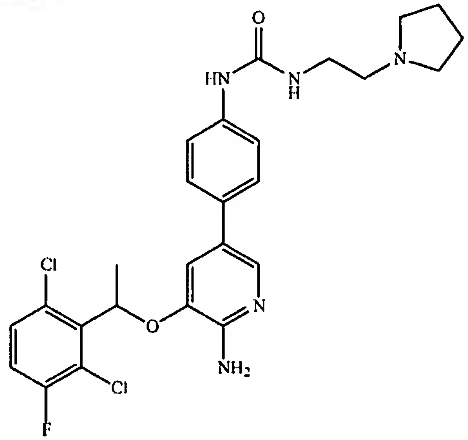
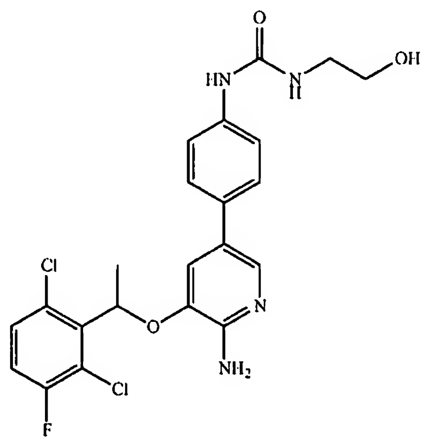
I-372		1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea	0.21	10 as in Example I-371		532 [M + 1]
I-373		1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea	0.064	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.68(s, 2H), 7.45(m, 2H), 7.36(d, 2H), 7.25(m, 2H), 6.95(s, 2H), 6.55(q, 1H), 4.88(s, 2H), 3.83(t, 2H), 3.31(m, 3H), 1.87 (d, 3H).	479 [M + 1]

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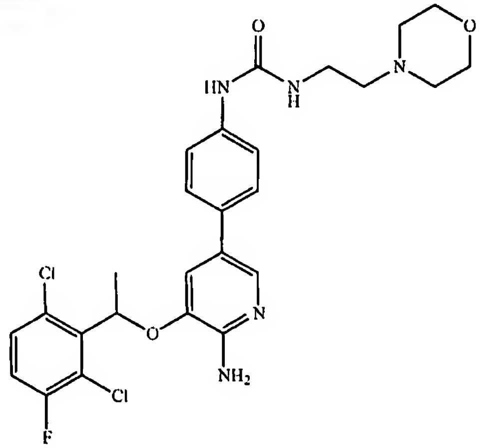
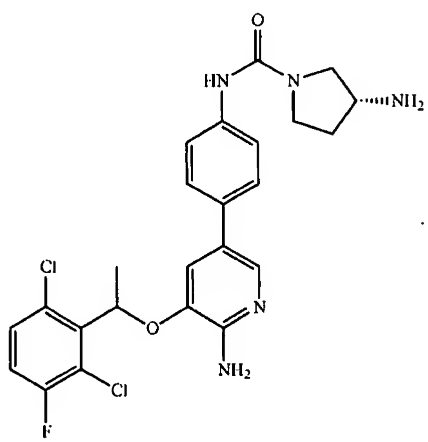
I-374		1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea	0.062	10 as in Example I-371	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.55(m, 3H), 7.35(d, 2H), 7.23(m, 3H), 6.95(s, 1H), 6.55(q, 1H), 4.86(s, 2H), 3.71(t, 2H), 3.31(m, 6H), 2.51 (m, 4H), 1.88(d, 3H).	548.2 [M + 1]
I-375		(R)-3-Amino-pyrrolidine-1-carboxylix acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.053	10 as in Example I-371	(300 MHz, CDCl3) δ 7.65(m, 4H), 7.31(m, 3H), 7.19(m, 2H), 6.37(m, 1H), 4.87(s, 2H), 3.95(m, 1H), 3.80(m, 1H), 3.60(m, 2H), 3.31(m, 2H), 2.45 (m, 1H), 2.18(m, 1H), 1.95(d, 3H).	503.8 [M + 1]

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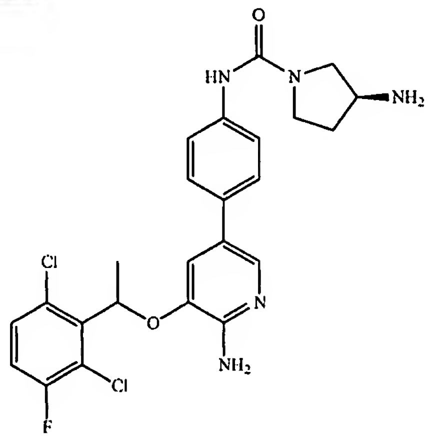
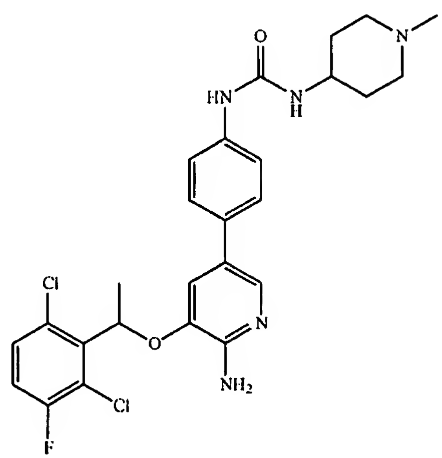
I-376		(S)-3-Amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.052	10 as in Example I-371	(300 MHz, CDCl3) δ 7.85(m, 4H), 7.31(m, 3H), 7.19(m, 2H), 6.37(m, 1H), 4.87(s, 2H), 3.95(m, 1H), 3.80(m, 1H), 3.60(m, 2H), 3.31(m, 2H), 2.45 (m, 1H), 2.18(m, 1H), 1.95(d, 3H).	504.1 [M + 1]
I-377		1-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-pipendin-4-yl)-urea	0.04	10 as in Example I-371		534 [M + 1]

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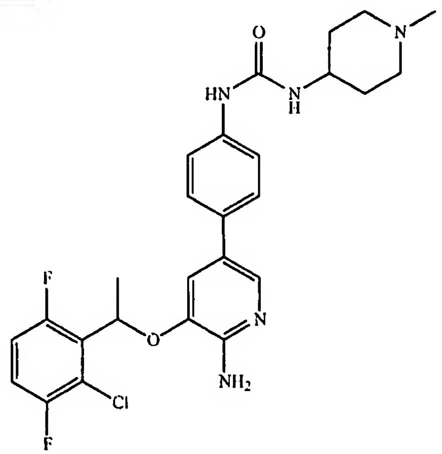
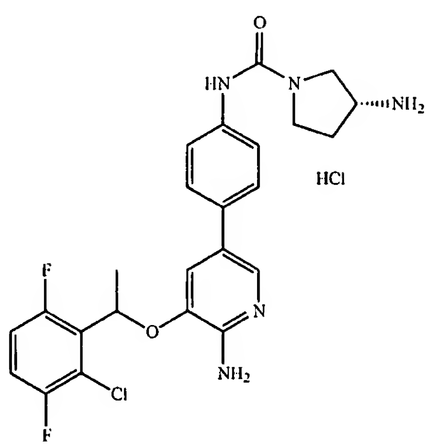
I-378		1-(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-pipendin-4-yl)-urea	0.038	10 as in Example I-371	518 [M + 1]
I-379		(R)-3-Amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.069	10 as in Example I-371	488 [M + 1]

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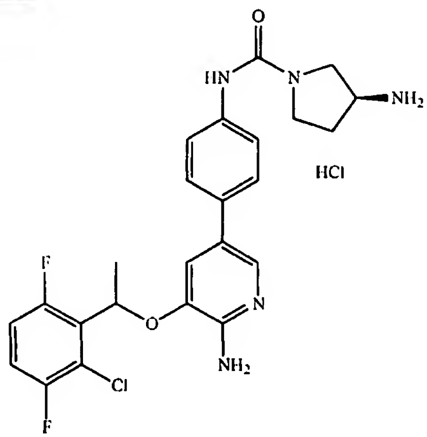
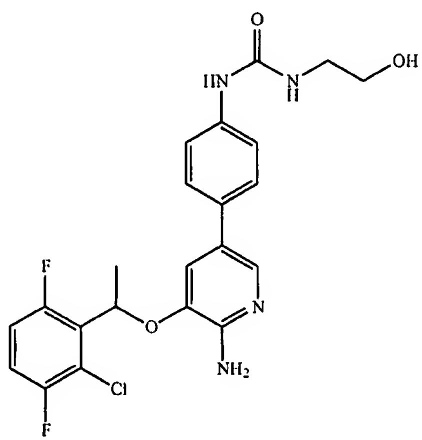
I-380		(S)-3-Amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy}-pyridin-3-yl}-phenyl)-amide	0.075	10 as in Example I-371		488 [M + 1]
I-381		1-(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea	0.11	10 as in Example I-371	(300 MHz, CDCl3) δ 7.69(d, 2H), 7.37(d, 2H), 7.25(d, 2H), 7.15(m, 2H), 7.09(d, 2H), 6.00(q, 1H), 4.86(s, 2H), 3.63(t, 2H), 3.32(m, 3H), 1.83 (d, 3H).	463 [M + 1]

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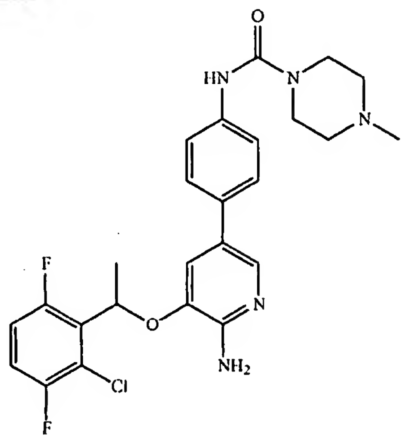
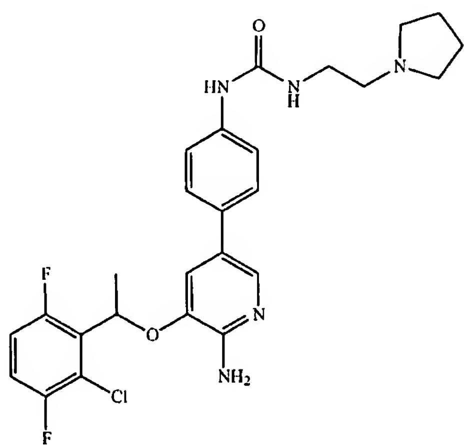
I-382		4-Methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amine	0.082	10 as in Example I-371	(300 MHz, CDCl3) δ 7.78(s, 1H), 7.41(d, 2H), 7.29(d, 2H), 7.09(s, 1H), 7.05(m, 1H), 6.95(m, 1H), 6.56 (bs, 1H), 6.00(q, 1H), 5.25(s, 2H), 3.58(m, 4H), 2.53(m, 4H), 2.38 (s, 3H), 1.84(d, 3H).	502 [M + 1]
I-383		1-(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea	0.11	10 as in Example I-371		516 [M + 1]

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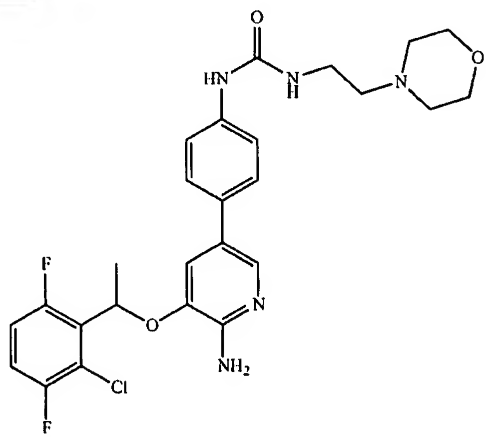
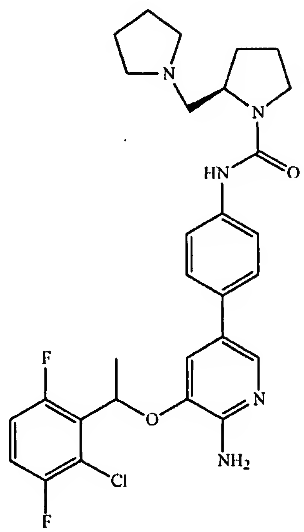
I-384		1-(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea	0.13	10 as in Example I-371	(300 MHz, CDCl3) δ 7.83(d, 1H), 7.29(m, 5H), 7.00(m, 4H), 5.94(q, 1H), 4.87(bs, 2H), 3.67(m, 4H), 3.38 (m, 2H), 2.52(m, 4H), 1.86(d, 3H).	533.7 [M + 1]
I-385		(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide	0.13	10 as in Example I-371	(300 MHz, CDCl3) δ 7.93(s, 1H), 7.67(d, 2H), 7.27(d, 2H), 6.95(m, 4H), 6.70(q, 1H), 4.84(s, 2H), 3.85 (m, 1H), 3.75(m, 1H), 3.40(m, 1H), 2.90(m, 4H), 2.65(m, 4H), 2.10 (m, 3H), 1.85(d, 3H), 1.9–1.7 (m, 3H).	555.8 [M + 1]

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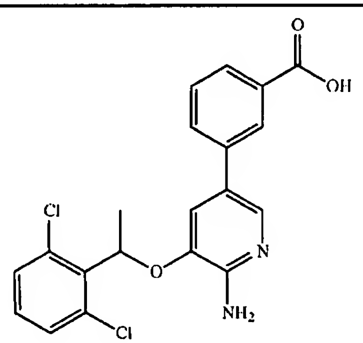
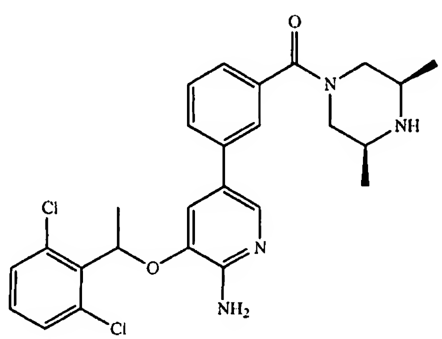
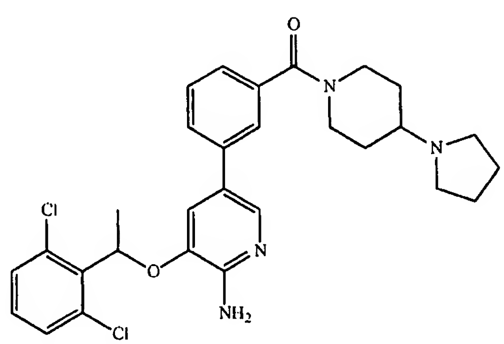
I-386		3-(6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		3 as in Example I-211		403 [M + 1]
I-387		(3-{6-Aminno-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.16	4	(300 MHz, CDCl3) δ 7.86(s, 1H), 7.39(m, 4H), 7.31(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(m, 1H), 4.93(s, 2H), 4.65(m, 1H), 3.56(m, 1H), 2.95(m, 1H), 2.79(m, 1H), 2.71(m, 1H), 2.44(m, 1H), 1.84 (d, 3H), 1.95(m, 1H), 1.25(d, 3H), 1.17(d, 3H).	501 [M + 1]
I-388		(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.1	4 as in Example I-387	(300 MHz, CDCl3) δ 7.85(s, 1H), 7.39(m, 4H), 7.32(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(m, 1H), 4.90(s, 2H), 4.65(m, 1H), 3.65(m, 1H), 3.05(m, 2H), 2.80(m, 1H), 2.65(m, 4H), 2.30(m, 1H), 2.05 (m, 1H), 1.86(d, 3H), 1.81(m, 3H), 1.52(m, 4H).	539 [M + 1]

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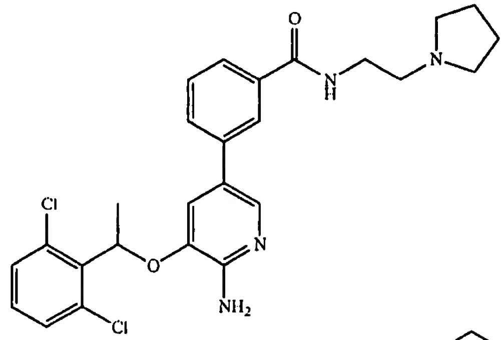
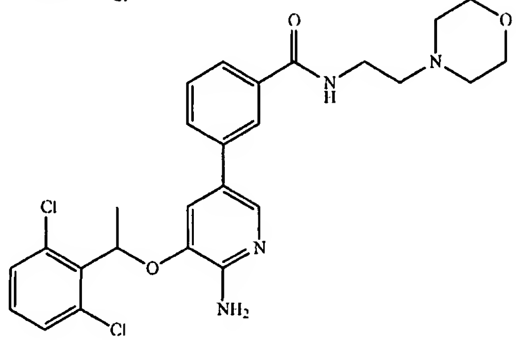
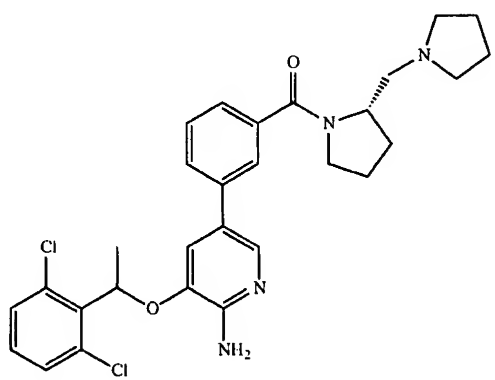
I-389		3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.13	4 as in Example I-387	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.82(s, 1H), 7.69(d, 1H), 7.45(m, 3H), 7.32(d, 2H), 7.15(t, 1H), 7.06(s, 1H), 6.99(bm, 1H), 6.16(q, 1H), 4.93(s, 2H), 3.61(m, 2H), 2.78(m, 2H), 2.63(m, 4H), 1.87(d, 3H), 1.82 (m, 4H).	501 [M + 1]
I-390		3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.12	4 as in Example I-387	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.82(s, 1H), 7.65(d, 1H), 7.48(m, 3H), 7.32(d, 2H), 7.15(t, 1H), 7.06(s, 1H), 6.78 (bm, 1H), 6.16(q, 1H), 4.95(s, 2H), 3.73(m, 4H), 3.59(m, 2H), 2.62(m, 2H), 2.51(m, 4H), 1.87(d, 3H).	517 [M + 1]
I-391		(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.098	4 as in Example I-387	(300 MHz, CDCl3) δ 7.86(d, 1H), 7.37(m, 4H), 7.30(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(m, 1H), 4.91(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.84(d, 3H), 1.70-2.0 (m, 10H)	541 [M + 1]

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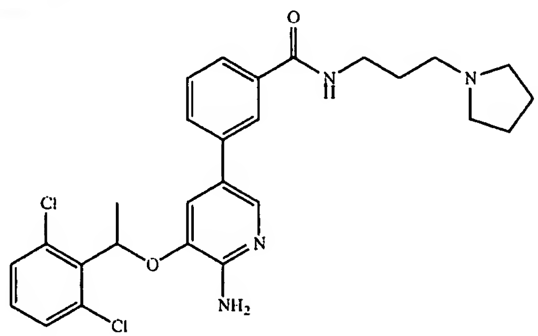
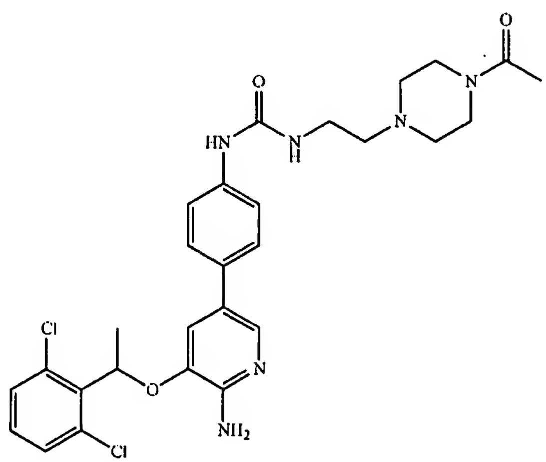
I-392		3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.072	4 as in Example I-387	(300 MHz, CDCl3) δ 8.60 (bm, 1H), 7.89(s, 1H), 7.65(d, 1H), 7.45(m, 3H), 7.32(d, 2H), 7.15(t, 1H), 7.04(s, 1H), 6.17(q, 1H), 4.89(s, 2H), 3.62(m, 2H), 2.78(m, 2H), 2.66(m, 4H), 1.86(d, 3H), 1.83(m, 2H), 1.79(m, 4H).	513 [M + 1]
I-393		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide	0.079	4 as in Example I-387	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.81(s, 1H), 7.63(d, 1H), 7.48(m, 3H), 7.32(d, 2H), 7.15(t, 1H), 7.06(s, 1H), 6.69 (bm, 1H), 6.16(q, 1H), 4.94(s, 2H), 3.65(m, 4H), 3.50(m, 2H), 2.62(m, 2H), 2.52(m, 4H), 2.09(s, 3H), 1.87(d, 3H).	556 [M + 1]

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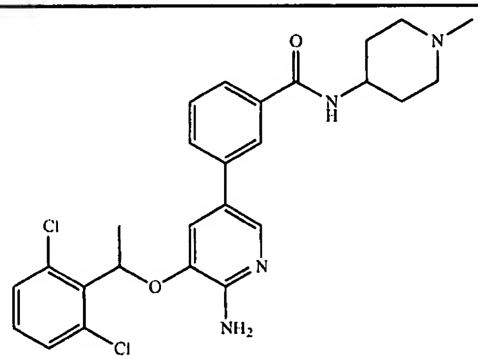
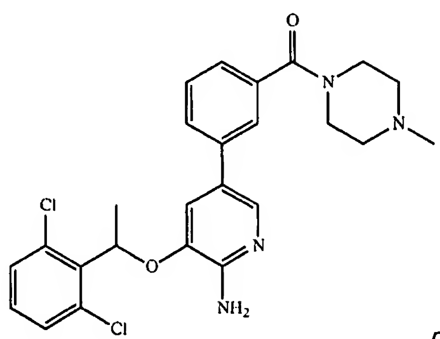
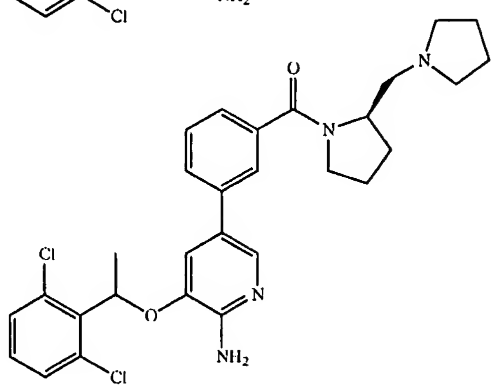
I-394		3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.061	4 as in Example I-387	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.73(s, 1H), 7.65(d, 1H), 7.50(d; 1H), 7.43(t, 1H), 7.32(d, 2H), 7.16(t, 1H), 7.04(s, 1H), 6.15(m, 1H), 6.05 (bd, 1H), 4.92(s, 2H), 4.03(m, 1H), 2.94(m, 2H), 2.38(s, 3H), 2.26(m, 2H), 2.09(m, 2H), 1.86 (d, 3H), 1.70(m, 2H).	499 [M + 1]
I-395		(3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.058	4 as in Example I-387	(300 MHz, CDCl3) δ 7.85(s, 1H), 7.40(m, 4H), 7.30(d, 2H), 7.16(t, 1H), 7.02(s, 1H), 6.15(m, 1H), 4.93(s, 2H), 3.82(m, 2H), 3.45(m, 2H), 2.52(m, 2H), 2.38(m, 2H), 2.33(s, 3H), 1.86(d, 2H).	487 [M + 1]
I-396		(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.18	4 as in Example I-387	(300 MHz, CDCl3) δ 7.86(d, 1H), 7.37(m, 4H), 7.30(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(m, 1H), 4.91(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.84(d, 3H), 1.70–2.0(m, 10H)	541 [M + 1]

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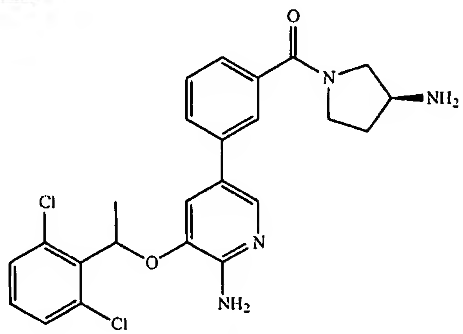
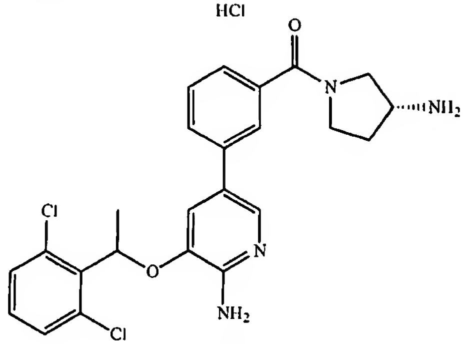
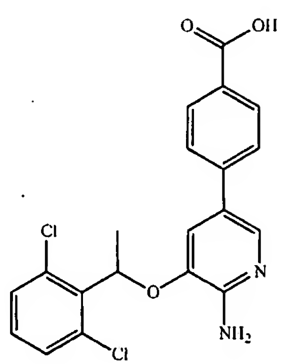
I-397	 HCl	(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone	0.055	4 as in Example I-387	(300 MHz, CD3OD) δ 7.74(s, 1H), 7.69–7.43(m, 6H), 7.32(t, 1H), 7.22(s, 1H), 6.42(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18 (m, 1H), 1.90(d, 3H).	471 [M + 1]
I-398	 HCl	(3-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.072	4 as in Example I-387	(300 MHz, CD3OD) δ 7.74(s, 1H), 7.69–7.43(m, 6H), 7.32(t, 1H), 7.22(s, 1H), 6.42(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18 (m, 1H), 1.90(d, 3H).	471 [M + 1]
I-399		4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid		3 as in Example I-211		403 [M + 1]

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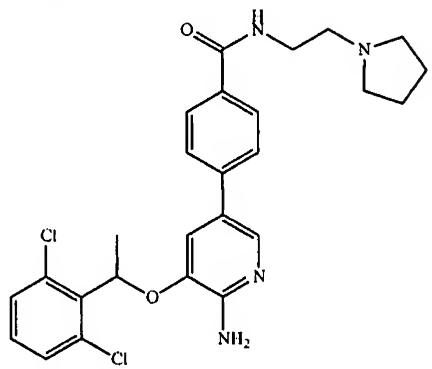
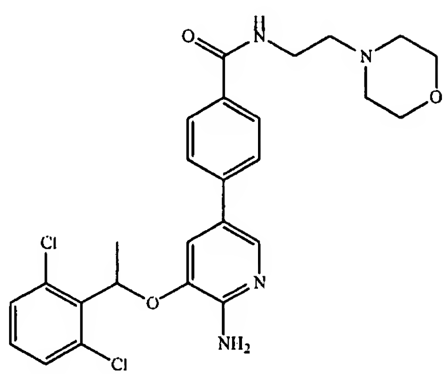
I-400		4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.059	4	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.79 (d, 2H), 7.43(d, 2H), 7.32(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.87 (bm, 1H), 6.15(q, 1H), 4.93(s, 2H), 3.58(m, 2H), 2.72(m, 2H), 2.58(m, 4H), 1.87(d, 3H), 1.80(m, 4H).	501 [M + 1]
I-401		4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.073	4 as in Example I-400	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.79 (d, 2H), 7.44(d, 2H), 7.32(d, 2H), 7.15(t, 1H), 7.03(s, 1H), 6.77 (bm, 1H), 6.15(q, 1H), 4.95(s, 2H), 3.74(m, 4H), 3.57(m, 2H), 2.61(m, 2H), 2.52(m, 4H), 1.87(d, 3H).	515 [M + 1]

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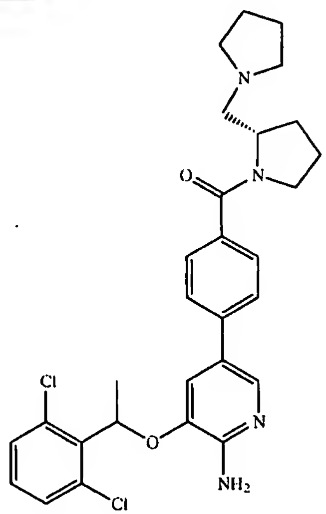
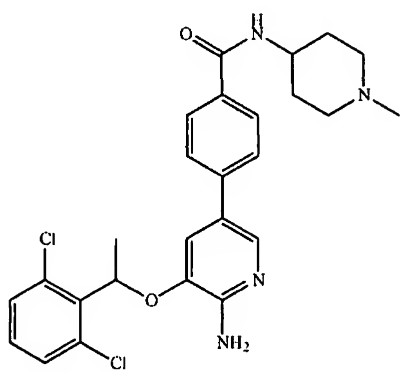
I-402		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.068	4 as in Example I-400	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.52(m, 2H), 7.39(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 7.01(s, 1H), 6.15(q, 1H), 4.91(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.86(d, 3H), 1.70–2.0(m, 10H)	539 [M + 1]
I-403		4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.062	4 as in Example I-400	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.76(d, 2H), 7.42(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(q, 1H), 5.97 (bd, 1H), 4.94 (s, 2H), 4.03(m, 1H), 2.85(m, 2H), 2.32(s, 3H), 2.18(m, 2H), 2.06(m, 2H), 1.86(d, 3H), 1.60(m, 2H).	501 [M + 1]

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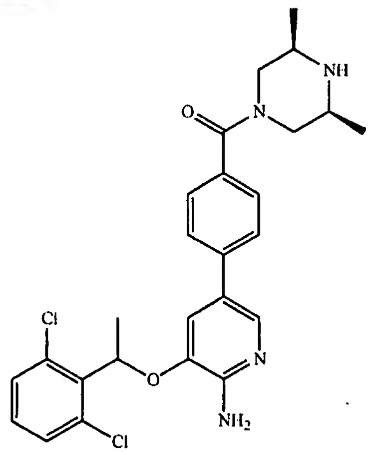
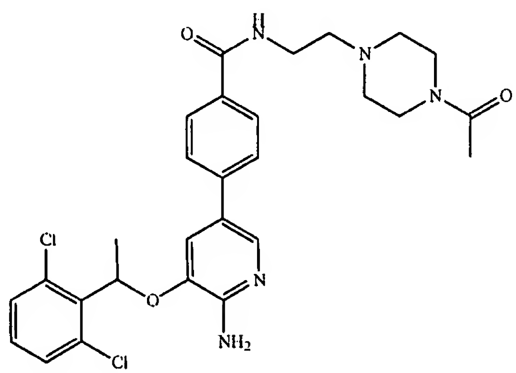
I-404		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.052	4 as in Example I-400	(300 MHz, CDCl3) δ 7.88(s, 1H), 7.41(m, 4H), 7.32(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(q, 1H), 4.92(s, 2H), 4.62(m, 1H), 3.66 (m, 1H), 2.82(m, 2H), 2.68(m, 1H), 2.40(m, 1H), 1.87(d, 3H), 1.65 (m, 1H), 1.15(d, 3H), 0.98(d, 3H).	499 [M + 1]
I-405		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide	0.062	4 as in Example I-400	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.78(d, 2H), 7.44(d, 2H), 7.32(d, 2H), 7.15(t, 1H), 7.03(s, 1H), 6.69 (bm, 1H), 6.15(q, 1H), 4.96 (s, 2H), 3.66(m, 2H), 3.61(m, 2H), 3.50(m, 2H), 2.62(m, 2H), 2.52(m, 4H), 2.10(s, 3H), 1.87(d, 3H).	556 [M + 1]

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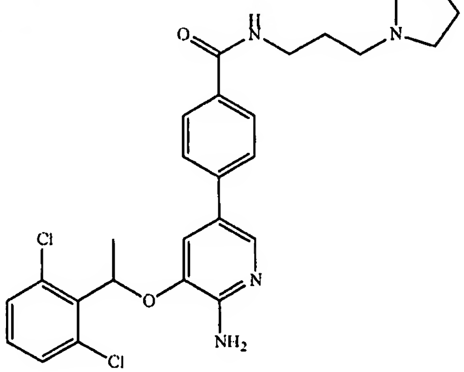
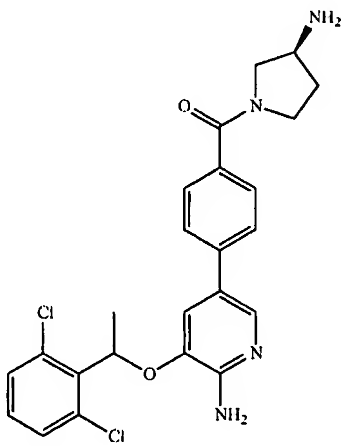
I-406		4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.061	4 as in Example I-400	(300 MHz, CDCl3) δ 8.80 (bm, 1H), 7.90(s, 1H), 7.79(d, 2H), 7.40(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 7.02(s, 1H), 6.15(q, 1H), 4.91 (s, 2H), 3.62(m, 2H), 2.78(m, 2H), 2.66(m, 4H), 1.87(d, 3H), 1.85 (m, 4H), 1.25(m, 2H).	513 [M + 1]
I-407	 HCl	(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone	0.05	4 as in Example I-400	(300 MHz, CD3OD) δ 7.74–7.24(m, 9H), 6.39(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	471 [M + 1]

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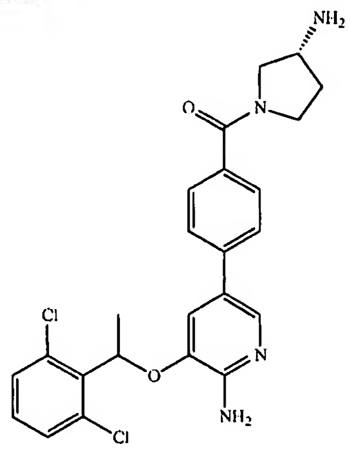
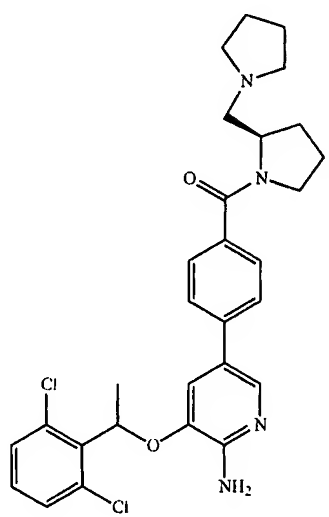
I-408	 HCl	(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.049	4 as in Example I-400	(300 MHz, CD3OD) δ 7.74–7.24(m, 9H), 6.39(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	471 [M + 1]
I-409		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.081	4 as in Example I-400	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.52(m, 2H), 7.39(d, 2H), 7.31(d, 2H), 7.15 (t, 1H), 7.01(s, 1H), 6.15(q, 1H), 4.91(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.86(d, 3H), 1.70–2.0(m, 10H)	539 [M + 1]

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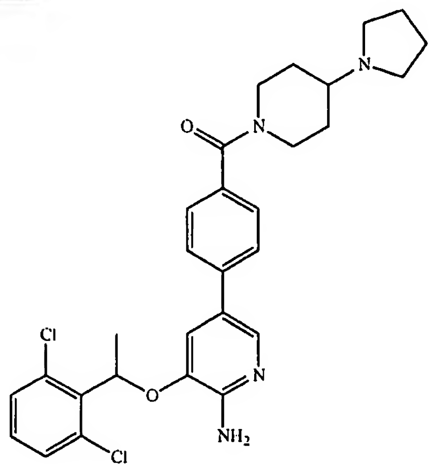
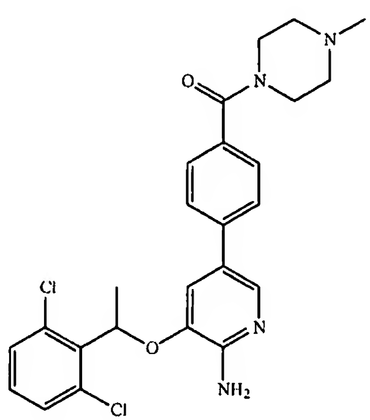
I-410		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.055	4 as in Example I-400	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.39(m, 4H), 7.32(d, 2H), 7.17(t, 1H), 7.01 (s, 1H), 6.15(q, 1H), 4.91(s, 2H), 4.60(m, 1H), 3.76(m, 1H), 3.00(m, 2H), 2.60(m, 4H), 2.28(m, 1H), 1.95(m, 2H), 1.86(d, 3H), 1.81(m, 4H), 1.56(m, 2H).	541 [M + 1]
I-411		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.053	4 as in Example I-400	(300 MHz, CDCl3) δ 7.87(s, 1H), 7.40(m, 4H), 7.31(d, 2H), 7.15(t, 1H), 7.01 (s, 1H), 6.15(q, 1H), 4.92(s, 2H), 3.78(m, 2H), 3.52(m, 2H), 2.41(m, 4H), 2.34(s, 3H), 1.86(d, 3H).	487 [M + 1]

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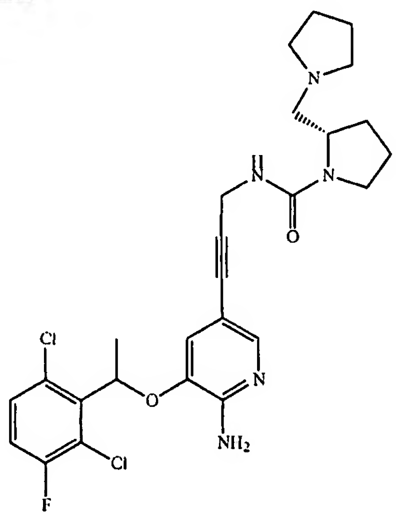
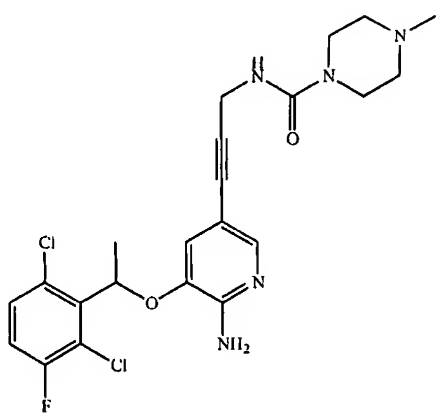
I-412		(S)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide	0.067	11	(300 MHz, CDCl3) δ 9.05(br, 1H), 7.70(s, 1H), 7.05(t, 1H), 6.70(s, 1H), 6.02 (q, 1H), 5.01(s, 2H), 4.15(dd, 2H), 3.75(m, 2H), 3.25(m, 1H), 2.75(m, 3H), 2.45(m, 3H), 2.05(m, 1H), 1.78(d, 3H), 1.65(br, 7H).	534 [M + 1]
I-413		4-Methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide	0.056	11	(300 MHz, CDCl3) δ 7.75(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.75(s, 1H), 6.02(q, 1H), 5.01(s, 2H), 4.20(d, 2H), 3.45(m, 4H), 2.45(m, 4H), 2.25(s, 3H), 1.81(d, 3H).	480 [M + 1]

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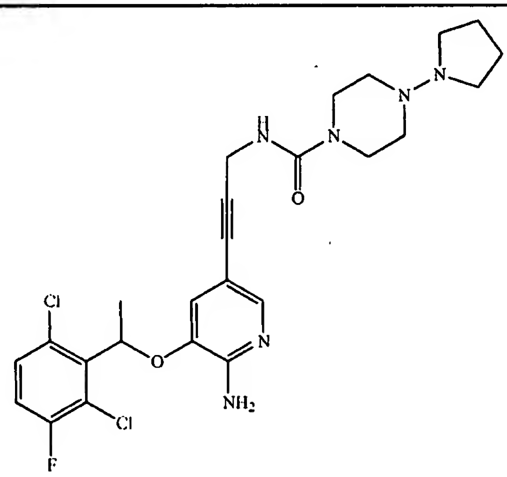
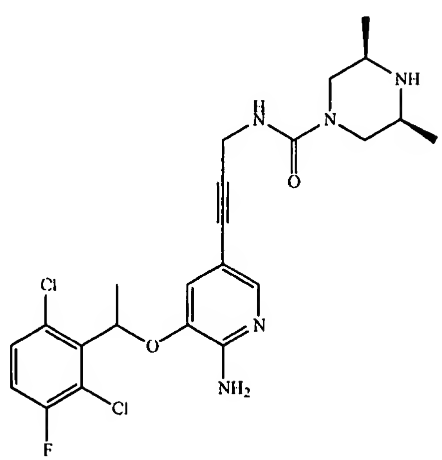
I-414		4-Pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide	0.058	11	(300 MHz, CDCl3) δ 7.75(s, 1H), 7.30(m, 2H), 7.10(t, 1H), 6.70(s, 1H), 6.02(q, 1H), 5.01(s, 2H), 4.20(d, 2H), 3.89(d, 1H) 2.89(t, 2H), 2.55(s, 4H), 2.21(m, 2H), 1.90(d, 2H), 1.81 (d, 3H), 1.45(m, 2H), 1.25(m, 2H).	534 [M + 1]
I-415		(3R,5S)-3,5-Dimethyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-amide	0.063	11	(300 MHz, CDCl3) δ 7.75(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.75(s, 1H), 6.02(q, 1H), 5.01(s, 2H), 4.78(s, 1H), 4.20(d, 2H), 3.85(d, 1H), 2.85(m, 4H), 2.45(t, 1H), 1.89(s, 3H), 1.01(d, 6H).	494 [M + 1]

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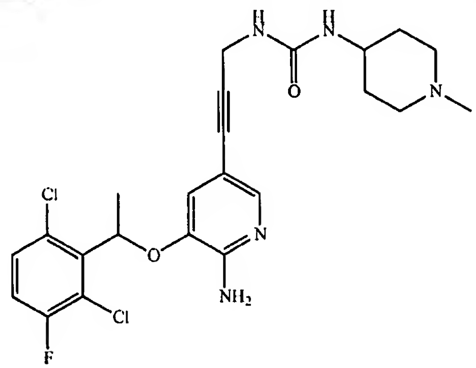
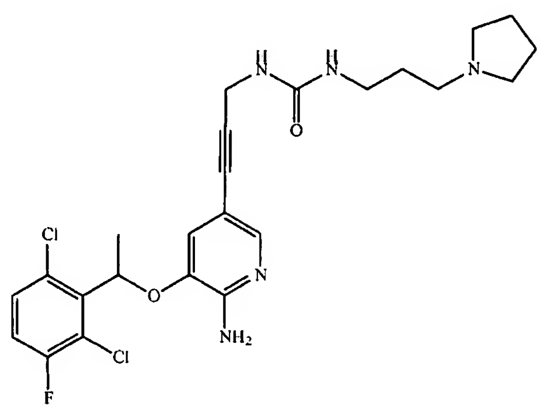
I-416		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(1-methyl-piperidin-4-yl)-urea	0.051	11	(300 MHz, CDCl3) δ 7.75(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.70(s, 1H), 6.00(q, 1H), 5.25(m, 1H), 5.05(s, 2H), 4.80(d, 1H), 4.15(d, 2H), 2.75(d, 2H), 2.20(s, 3H), 2.10(t, 2H), 1.95(d, 2H), 1.75 (d, 3H), 1.45(d, 2H).	494 [M + 1]
I-417		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(3-pyrrolidin-1-yl-propyl)-urea	0.062	11	(300 MHz, CDCl3) δ 7.70(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.70(s, 1H), 6.00(q, 1H), 5.30(m, 1H), 5.01(s, 2H), 4.15(d, 2H), 3.25(m, 2H), 2.50(m, 6H), 1.80(d, 3H), 1.82(m, 4H), 1.60(m, 2H).	508 [M + 1]

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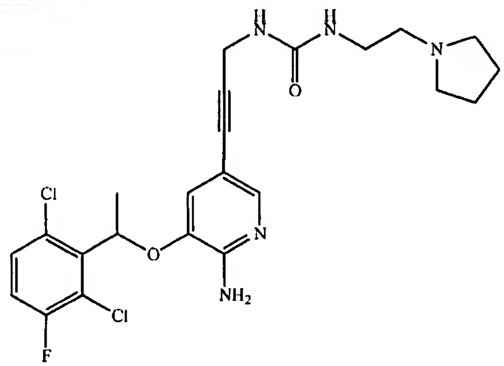
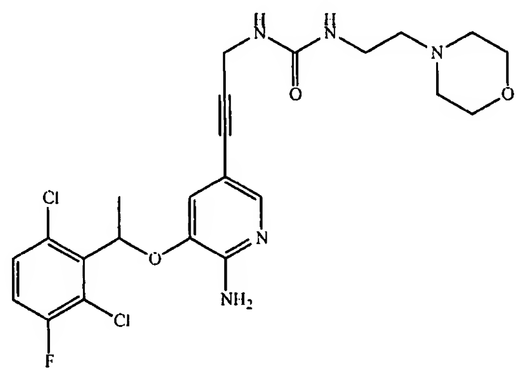
I-418		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea	0.052	11	(300 MHz, CDCl3) δ 7.70(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.70(s, 1H), 6.00(q, 1H), 5.45(s, 1H), 5.15(s, 2H), 4.15(d, 2H), 3.25(m, 2H), 2.60(t, 2H), 2.50(m, 4H), 1.80(d, 3H), 1.70(s, 4H).	496 [M + 1]
I-419		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl-urea	0.055	11	(300 MHz, CDCl3) δ 7.73(s, 1H), 7.28(m, 2H), 7.05(t, 1H), 6.70(s, 1H), 6.00(q, 1H), 5.25(s, 1H), 5.15(s, 2H), 4.15(d, 2H), 3.65(m, 4H), 3.25(m, 2H), 2.45(m, 6H), 1.80(d, 3H).	510 [M + 1]

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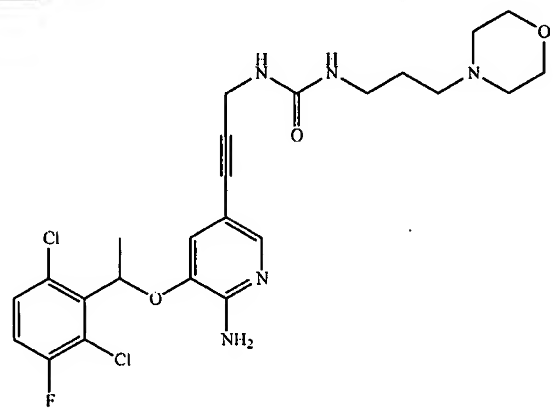
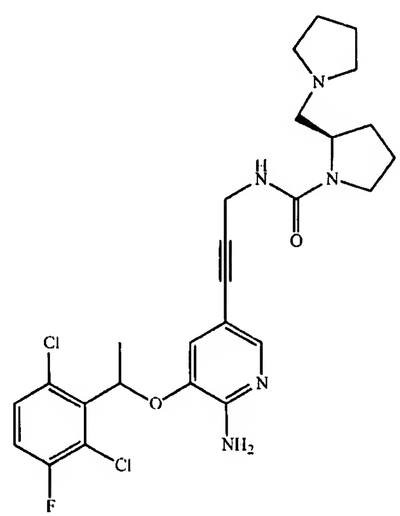
I-420		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-3-(3-morpholin-4-yl-propyl)-urea	0.064	11	(300 MHz, CDCl3) δ 7.70(s, 1H), 7.30(m, 2H), 7.05(t, 1H), 6.70(s, 1H), 6.00(q, 1H), 5.10(s, 2H), 4.15(d, 2H), 3.70(m, 6H), 3.20(s, 2H), 2.50(m, 4H), 1.80(d, 3H), 1.65(m, 2H).	524 [M + 1]
I-421		(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidin3-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl-amide	0.071	11	(300 MHz, CDCl3) δ 9.05(br, 1H), 7.70(s, 1H), 7.05(t, 1H), 6.70(s, 1H), 6.02(q, 1H), 5.01(s, 2H), 4.15(dd, 2H), 3.75(m, 2H), 3.25(m, 1H), 2.75(m, 3H), 2.45(m, 3H), 2.05(m, 1H), 1.78(d, 3H), 1.65(br, 7H).	534 [M + 1]

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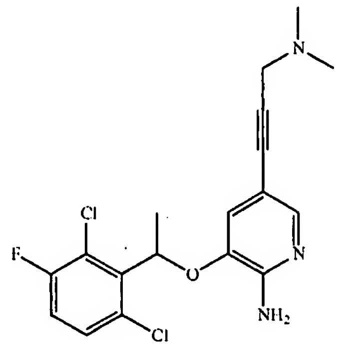
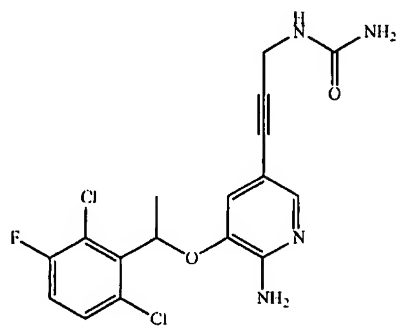
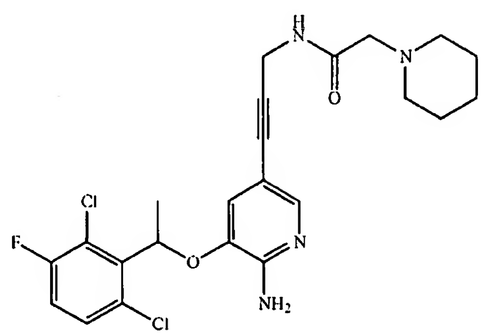
I-422		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-dimethylamino-prop-1-ynyl)-pyridin-2-ylamine	0.071	11		382 [M + 1]
I-423		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-area	0.062	11		397 [M + 1]
I-424		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-piperidin-1--yl-acetamide	0.016	12	(300 MHz, CDCl3) δ 7.74(s, 1H), 7.45 (bm, 1H), 7.31(dd, 1H), 7.07(t, 1H), 6.73(s, 1H), 6.00(q, 1H), 4.99(s, 2H), 4.26(d, 2H). 2.98(s, 2H), 2.46(m, 4H), 1.81(d, 3H), 1.59(m, 4H), 1.45(m, 2H).	579 [M + 1]

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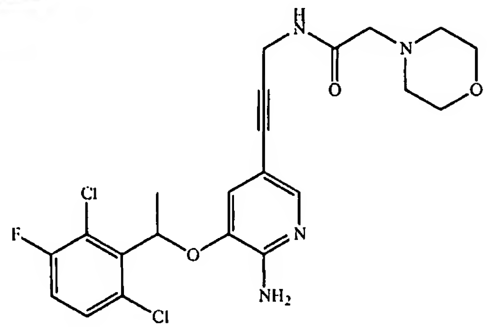
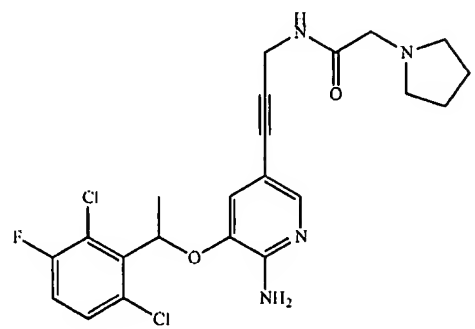
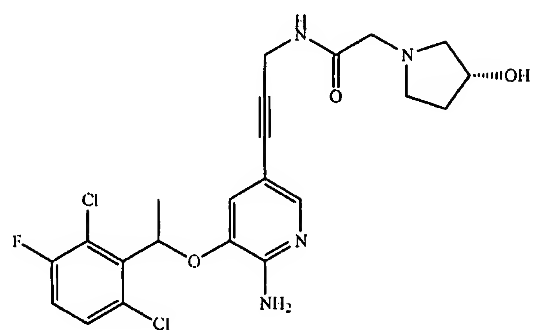
I-425		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-morpholin-4-yl-acetamide	0.027	12	(300 MHz, CDCl3) δ 7.74(s, 1H), 7.45 (bm, 1H), 7.31(m, 2H), 7.08(t, 1H), 6.71(s, 1H), 6.00(q, 1H), 5.02(s, 2H), 4.27(d, 2H), 3.73(m, 4H), 3.05(s, 2H), 2.54(m, 4H), 1.81(d, 3H).	481 [M + 1]
I-426		N-(3-{8-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-pyrrolidin-1-yl-acetamide	<0.0091	12	(300 MHz, CDCl3) δ 7.74(s, 1H), 7.37 (bm, 1H), 7.31(dd, 1H), 7.08(t, 1H), 6.72(s, 1H), 6.00(q, 1H), 5.01(s, 2H), 4.27(d, 2H), 3.18(s, 2H), 2.63(m, 4H), 2.01(m, 2H), 1.81(d, 3H), 1.80(m, 2H).	465 [M + 1]
I-427		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-((R)-3-hydroxy-pyrrolidin-1-yl)-acetamide	0.011	12	(300 MHz, CDCl3) δ 7.71(s, 1H), 7.45 (bm, 1H), 7.31(dd, 1H), 7.07(t, 1H), 6.72(s, 1H), 5.99(q, 1H), 5.06(s, 2H), 4.42(m, 1H), 4.25(m, 2H), 3.21(s, 2H), 3.00(m, 1H), 2.80(m, 1H), 2.71(m, 1H), 2.45(m, 1H), 2.22(m, 1H), 1.79(d, 3H), 1.78 (m, 2H).	481 [M + 1]

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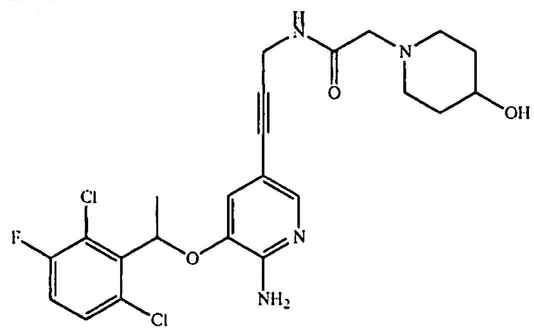
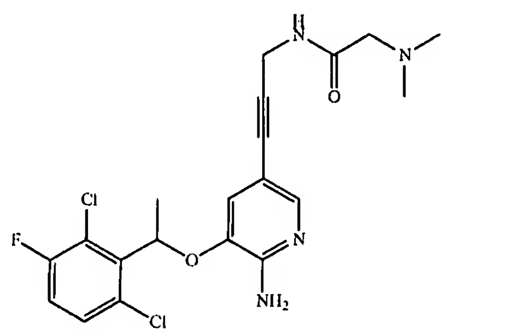
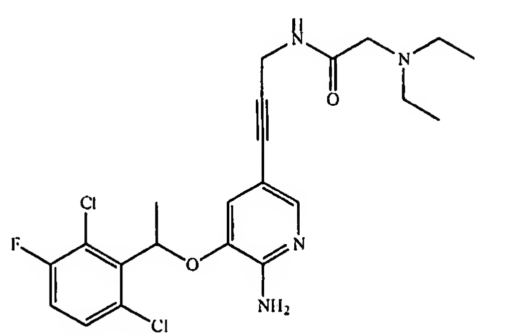
I-428		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-(4-hydroxy-piperidin-1-yl)-acetamide	0.012	12	(300 MHz, CDCl3) δ 7.73(d, 1H), 7.38 (bm, 1H), 7.31(dd, 1H), 7.08(dd, 1H), 6.72(d, 1H), 6.00(q, 1H), 5.03(s, 2H), , 4.26(d, 2H), 3.74(m, 1H), 3.02(s, 2H), 2.78(m, 2H), 2.32(m, 2H), 1.92(m, 4H), 1.80(d, 3H).	495 [M + 1]
I-429		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-dimethylamino-acetamide	0.022	12	(300 MHz, CDCl3) δ 7.73(d, 1H), 7.38 (bm, 1H), 7.31(dd, 1H), 7.08(dd, 1H), 6.72(d, 1H), 6.00(q, 1H), 4.99(s, 2H), 4.26(d, 2H), 2.98(s, 2H), 2.31(s, 6H), 1.80(d, 3H).	439 [M + 1]
I-430		N-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-prop-2-ynyl)-2-diethylamino-acetamide	0.013	12	(300 MHz, CDCl3) δ 7.73(d, 1H), 7.59 (bm, 1H), 7.30(dd, 1H), 7.07(dd, 1H), 6.72(d, 1H), 6.00(q, 1H), 4.98(s, 2H), 4.25(d, 2H), 3.05(s, 2H), 2.57(dd, 4H), 1.80(d, 3H), 1.03(t, 6H).	467 [M + 1]

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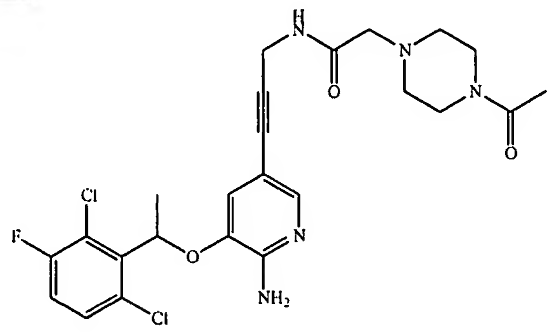
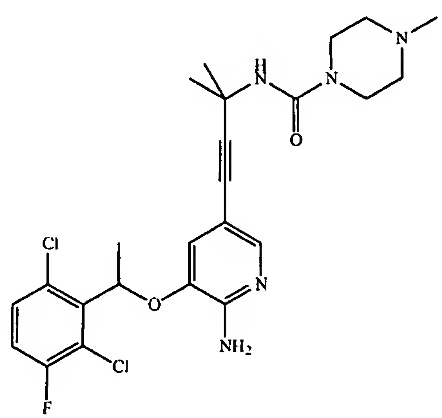
I-431		2-(4-Acetyl-piperazin-1-yl)-N-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]pyridin-3-yl}-prop-2-ynyl)-acetamide	0.027	12	(300 MHz, CDCl3) δ 7.73(d, 1H), 7.31(dd, 1H), 7.25 (bm, 1H), 7.08(dd, 1H), 6.71(d, 1H), 6.00(q, 1H), 5.04(s, 2H), , 4.27(d, 2H), 3.66(m, 2H), 3.52(m, 2H), 3.08(s, 2H), 2.78(m, 2H), 2.32(m, 2H), 2.53(m, 4H), 2.10(s, 3H), 1.81 (d, 3H).	522 [M + 1]
I-432		4-Methyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide	Ki 0.61	13 as in Example I-412	(300 MHz, CDCl3) δ 7.73(d, 1H), 7.30 (dd, 1H), 7.07(t, 1H), 6.78(d, 1H), 6.01(q, 1H), 5.01(s, 2H), 4.64(s, 1H), 3.38(m, 4H), 2.42(m, 4H), 2.31(s, 3H), 1.79(d, 3H), 1.70(s, 6H).	508 [M + 1]

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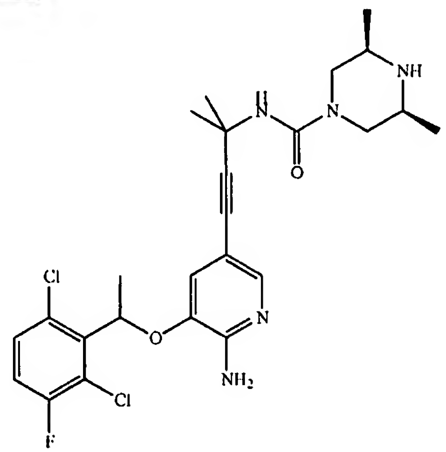
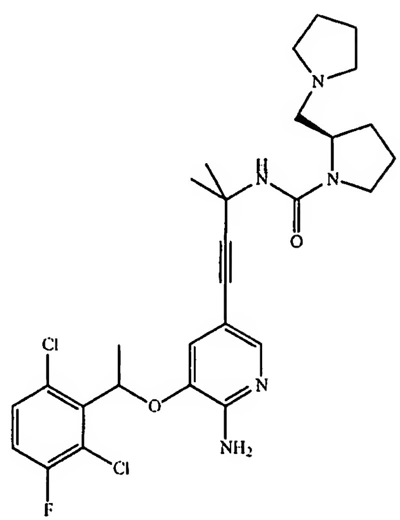
I-433		(3R,5S)-3,5-Dimethyl-piperazine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide	Ki 1.5	11	(300 MHz, CDCl3) δ 7.74(s, 1H), 7.30 (dd, 1H), 7.07(t, 1H), 6.79(s, 1H), 6.01(q, 1H), 4.93(s, 2H), 4.59(s, 1H), 3.75(m, 2H), 2.82(m, 2H), 2.35(m, 2H), 1.80(d, 3H), 1.71(s, 6H), 1.09(d, 6H).	522 [M + 1]
I-434		(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide	Ki 1.22	11	(300 MHz, CDCl3) δ 8.44(bs, 1H), 7.72 (d, 1H), 7.30(dd, 1H), 7.07(t, 1H), 6.79(s, 1H), 6.01(q, 1H), 4.87(s, 2H), 3.75(m, 1H), 3.25(m, 1H), 2.68(m, 2H), 2.56(m, 2H), 2.40(m, 1H), 2.05(m, 1H), 1.82–1.68 (m, 17H), 1.56(m, 1H).	562 [M + 1]

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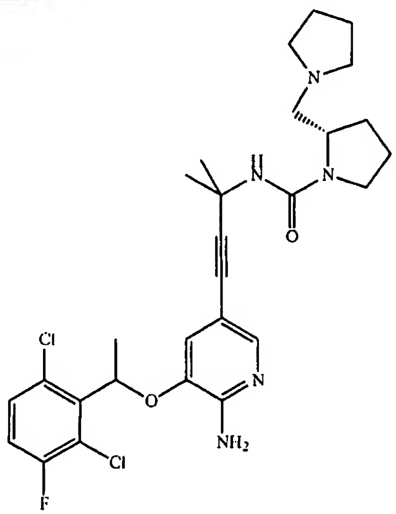
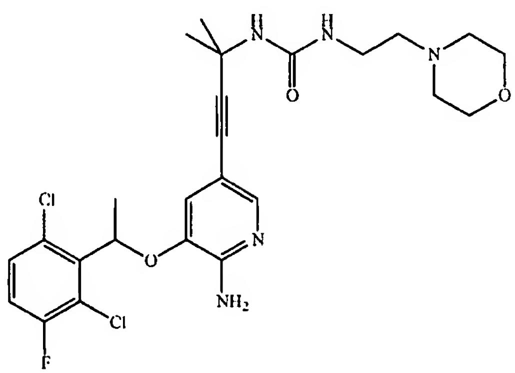
I-435		(S)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide	Ki 1.58	11	(300 MHz, CDCl3) δ 8.44(bs, 1H), 7.72 (s, 1H), 7.30(dd, 1H), 7.07(t, 1H), 6.79(s, 1H), 6.01(q, 1H), 4.87(s, 2H), 3.75(m, 1H), 3.25(m, 1H), 2.68(m, 2H), 2.56(m, 2H), 2.40(m, 1H), 2.05(m, 1H), 1.82–1.68 (m, 17H), 1.56(m, 1H).	562 [M + 1]
I-436		1-(3-{6-Amino-5-[1-(2,6-dicloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-morpholin-4-yl-ethyl)-urea	Ki 1.11	11	(300 MHz, CDCl3) δ 7.72(s, 1H), 7.31 (dd, 1H), 7.08(t, 1H), 6.75(s, 1H), 6.01(q, 1H), 5.53 (bm, 1H), 5.00(s, 2H), 4.66(bs, 1H), 3.56(m, 4H), 3.32(m, 2H), 2.45(m, 2H), 2.35(m, 4H), 1.81(d, 3H), 1.64(s, 6H).	538 [M + 1]

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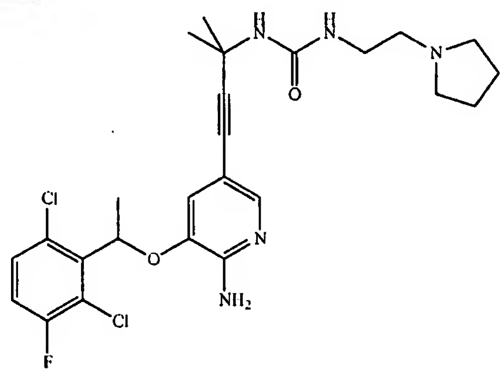
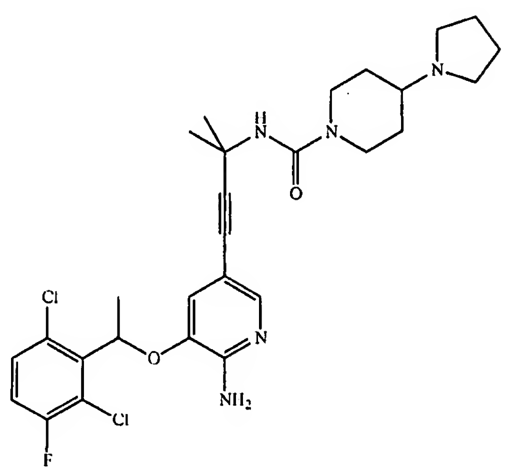
I-437		1-(3-{6-Amino-5-[1-(2,6-dicloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea	Ki 0.61	11	(300 MHz, CDCl3) δ 7.72(s, 1H), 7.31 (dd, 1H), 7.08(t, 1H), 6.77(s, 1H), 6.01(q, 1H), 5.68 (bm, 1H), 5.14(bs, 1H), 5.01(s, 2H), 3.30(m, 2H), 2.65(m, 2H), 2.50(m, 4H), 1.81(d, 3H), 1.68(m, 4H), 1.63(s, 6H).	522 [M + 1]
I-438		4-Pyrrolidin-1-yl-piperidine-1-carboxylic acid (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1,1-dimethyl-prop-2-ynyl)-amide	Ki 0.72	11	(300 MHz, CDCl3) δ 7.73(s, 1H), 7.31 (dd, 1H), 7.07(t, 1H), 6.79(s, 1H), 6.01(q, 1H), 5.68 (bm, 1H), 4.95(s, 2H), 4.68(bs, 1H), 3.88(m, 2H), 2.82(m, 2H), 2.58(m, 4H), 2.28(m, 1H), 1.92 (m, 2H), 1.81(d, 3H), 1.80(m, 4H), 1.70(s, 6H), 1.50(m, 2H).	562 [M + 1]

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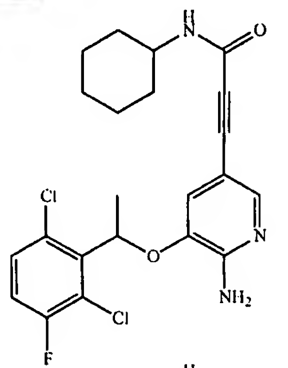
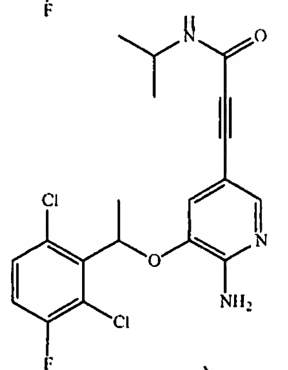
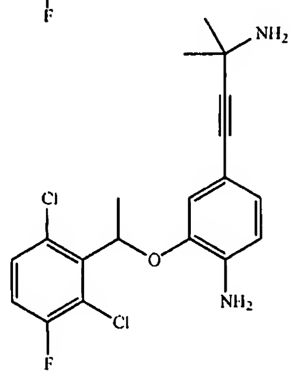
I-439		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid cyclohexylamide	Ki 0.46	11	(300 MHz, CDCl3) δ 7.85(d, 1H), 7.31 (dd, 1H), 7.09(t, 1H), 6.78(d, 1H), 6.00(q, 1H), 5.69 (bd, 1H), 5.14(s, 2H), 4.12 (m, 1H), 1.81(d, 3H), 1.20(d, 6H).	410 [M + 1]
I-440		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-propynoic acid isopropylamide	Ki 0.43	11	(300 MHz, CDCl3) δ 7.86(s, 1H), 7.31 (dd, 1H), 7.09(t, 1H), 6.79(s, 1H), 6.00(q, 1H), 5.72 (bd, 1H), 5.14(s, 2H), 3.82(m, 1H), 1.95(m, 2H), 1.80(d, 3H), 1.72(m, 2H), 1.65(m, 2H), 1.38(m, 2H), 1.20(m, 2H).	450 [M + 1]
I-441		4-(3-Amino-3-methyl-but-1-ynyl)-2-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-phenylamine	Ki 1.06	11	(300 MHz, CD3OD) δ 7.60(d, 1H), 7.45 (dd, 1H), 7.25(t, 1H), 6.66(d, 1H), 6.06(q, 1H), 1.84(d, 3H), 1.66(s, 6H).	382 [M + 1]

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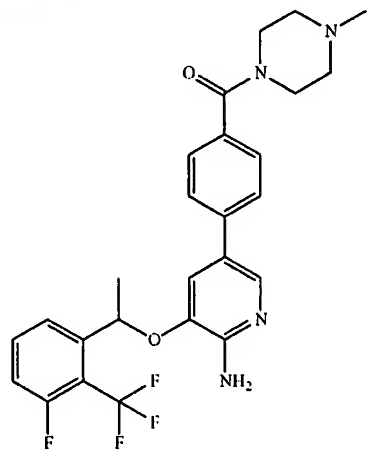
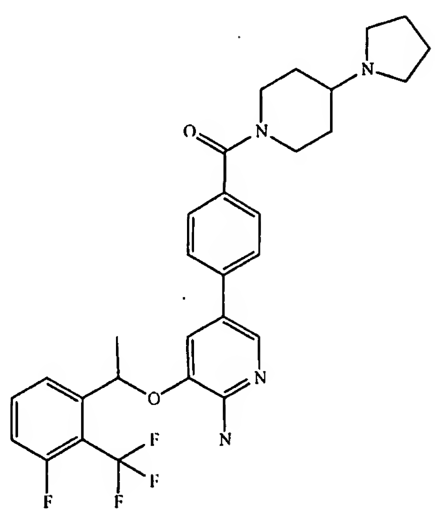
I-442		(4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	16% at 1 uM	13	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.51 (m, 1H), 7.40(m, 5H), 7.10(m, 1H), 6.90(s, 1H), 5.80(q, 1H), 4.94(s, 2H), 3.58(m, 4H), 2.53(m, 4H), 2.32(s, 3H), 1.84(d, 3H).	503 [M + 1]
I-443		(4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1yl)-methanone	13% at 1 um	13	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.54 (m, 1H), 7.32(d, 5H), 7.17(m, 1H), 6.90(d, 1H), 5.79(q, 1H), 4.93(s, 2H), 4.60(m, 1H), 3.80(m, 1H), 2.95(m, 2H), 2.64(m, 4H), 2.34(m, 1H), 1.95 (m, 2H), 1.81(m, 4H), 1.73(d, 3H), 1.56(m, 2H).	557 [M + 1]

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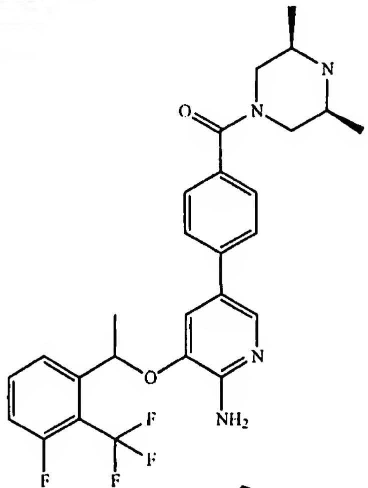
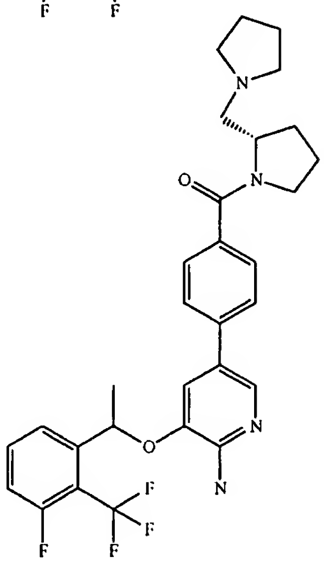
I-444		(4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	10% at 1 uM	13	(300 MHZ, CDCl3) δ 7.9(d, 1H), 7.50 (m, 1H), 7.36(m, 5H), 7.11(m, 1H), 6.90(s, 1H), 5.81(q, 1H), 4.93(s, 2H), 4.62(m, 1H), 3.66(m, 1H), 2.85(m, 2H), 2.65(m, 1H), 2.40(m, 1H), 1.73 (d, 3H), 1.10(m, 7H).	517 [M + 1]
I-445		(4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	15% at 1 uM	13	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.73 (m, 1H), 7.53(m, 3H), 7.34(d, 2H), 7.13(m, 1H), 6.90(s, 1H), 5.80(q, 1H), 4.93(s, 2H), 4.45(m, 1H), 3.50(m, 2H), 2.70(m, 4H), 1.73(d, 3H), 1.20–2.0(m, 10H).	557 [M + 1]

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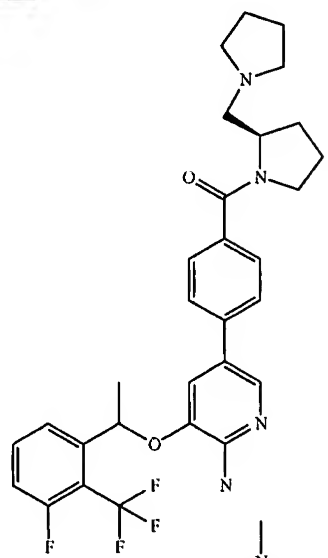
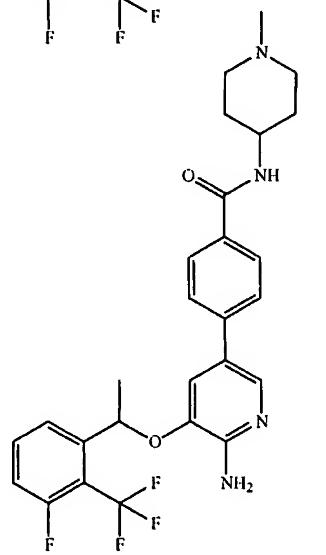
I-446		(4-{6 Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	12% at 1 uM	13	(300 MHz, CDCl3) δ 7.90(s, 1H), 7.73 (m, 1H), 7.53(m, 3H), 7.34(d, 2H), 7.13(m, 1H), 6.90(s, 1H), 5.80(q, 1H), 4.93(s, 2H), 4.45(m, 1H), 3.50(m, 2H), 2.70(m, 4H), 1.73(d, 3H), 1.20–2.0(m, 10H).	557 [M + 1]
I-449		4-[6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	12% at 1 uM	13	(300 MHz, CDCl3) δ 7.90(d, 1H), 7.75 (d, 2H), 7.72(m, 1H), 7.52(m, 1H), 7.48(d, 2H), 7.10(m, 1H), 6.89(d, 1H), 6.00 (bd, 1H), 5.80(q, 1H), 4.93 (s, 2H), 4.02(m, 1H), 2.85(m, 2H), 2.31 (s, 3H), 2.16(m, 2H), 2.05 (m, 2H), 1.73(d, 3H), 1.62(m, 2H).	517 [M + 1]

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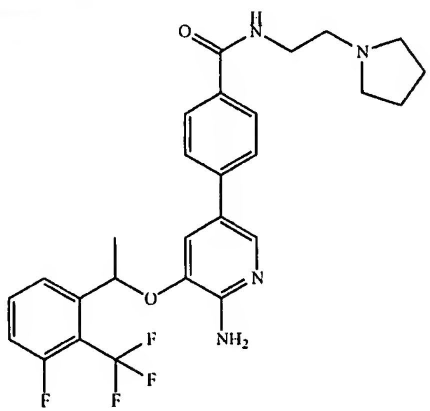
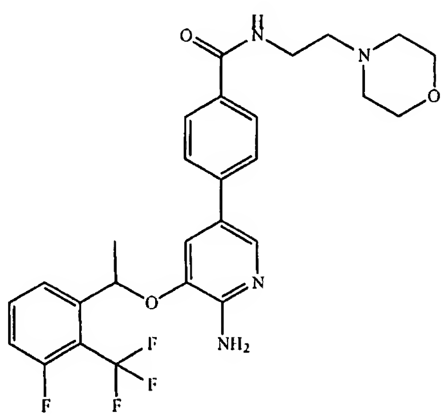
1-450		4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	7% at 1 uM	13	(300 MHz, CDCl3) δ 7.90(d, 1H), 7.79 (d, 2H), 7.55(m, 2H), 7.48(d, 2H), 7.13(m, 1H), 7.08(bs, 1H), 6.90(s, 1H), 5.80(q, 1H), 4.94(s, 2H), 3.58(m, 2H), 2.78(m, 2H), 2.62(m, 4H), 1.81(m, 4H), 1.72(d, 3H).	517 [M + 1]
1-451		4-{6-Amino-5-[1-(3-fluoro-3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	12% at 1 uM	13	(300 MHz, CDCl3) δ 7.91(d, 1H), 7.78 (d, 2H), 7.51(m, 2H), 7.39(d, 2H), 7.10(m, 1H), 6.91(d, 1H), 6.78(bs, 1H), 5.82(q, 1H), 4.97(s, 2H), 3.72(m, 4H), 3.57(m, 2H), 2.62(m, 2H), 2.52(m, 4H), 1.73(d, 3H).	533 [M + 1]

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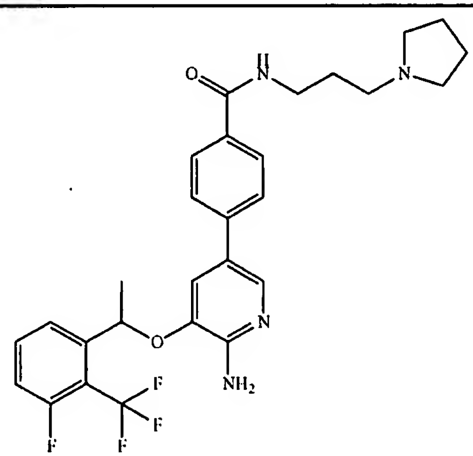
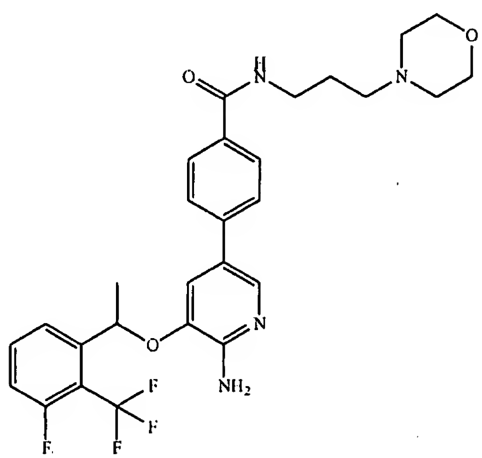
I-452		4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	3% at 1 uM	13	(300 MHz, CDCl3) δ 8.81(s, 1H), 7.92 (s, 1H), 7.78(d, 2H), 7.53(m, 1H), 7.48(d, 2H), 7.13(m, 1H), 6.90(s, 1H), 5.80(q, 1H), 4.90(s, 2H), 3.60(m, 2H), 2.78(m, 2H), 2.66(m, 4H), 1.85(m, 6H), 1.73(d, 3H).	531 [M + 1]
I-453		4-{6-Amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide	10% at 1 uM	13	(300 MHz, CDCl3) δ 7.93(s, 1H), 7.80 (d, 2H), 7.53(m, 3H), 7.38(d, 2H), 7.10(m, 1H), 6.91(d, 1H), 5.82(q, 1H), 4.95(s, 2H), 3.70(m, 4H), 3.57(m, 2H), 2.54(m, 6H), 1.81(m, 2H), 1.73(d, 3H).	547 [M + 1]

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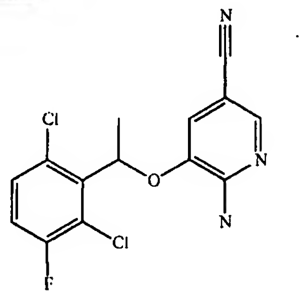
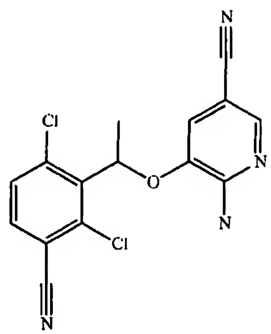
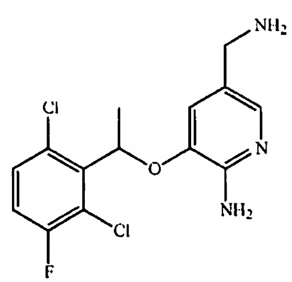
I-454		6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-nicotinonitrile	7% at 1 uM	Example I-454	(400 MHz, DMSO-d6) δ 7.93(s, 1H), 7.56 (m, 1H), 7.46(t, 1H), 6.88(br, 2H), 6.76(s, 1H), 6.02(q, 1H), 1.77(d, 3H).	325 [M − 1]
I-455		6-Amino-5-[1-(2,6-dichloro-3-cyano-phenyl)-ethoxy]-nicotinonitrile	6% at 1 uM	Example I-455	(400 MHz, DMSO-d6) δ 8.00(s, 1H), 7.81 (d, 1H), 7.07(t, 2H), 5.78(d, 1H), 1.74(d, 3H).	332 [M − 1]
I-456		5-Aminomethyl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine	0% at 1 uM	Example I-456	(400 MHz, DMSO-d6) δ 7.53(m, 1H), 7.43 (m, 2H), 6.76(s, 1H), 5.98(q, 1H), 5.47(br, 2H), 1.74(d, 3H)	331 [M + 1]

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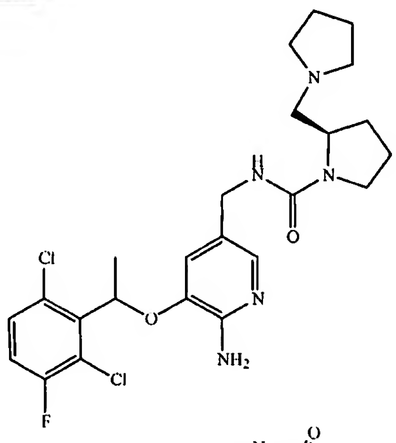
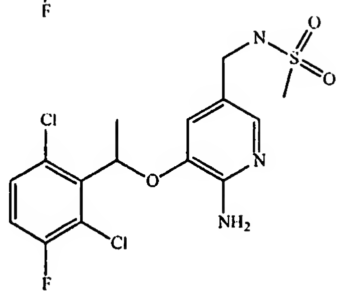
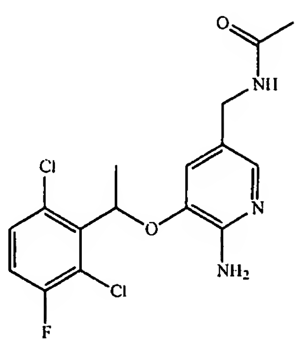
I-457		(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid {6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-amide	1% at 1 uM	Example I-457	(400 MHz, DMSO-d6) δ 9.58(s, 1H), 7.93 (s, 1H), 7.55(m, 1H), 7.40(s, 1H), 6.59(dd, 1H), 6.80(d, 1H), 6.06(t, 1H), 4.19(dd, 1H), 4.10(dd, 1H), 3.94(dd, 1H), 3.85(dd, 1H), 3.21(m, 2H), 3.15(m, 2H), 3.01(m, 2H), 1.98(m, 2H), 1.90(m, 2H), 1.84(m, 2H), 1.78(d, 3H), 1.72(br, 1H).	511 [M + 1]
I-458		N-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-methanesulfonamide	0% at 1 uM	as in Example I-13	(400 MHz, DMSO-d6) δ7.51(m, 1H), 7.43 (t, 2H), 7.28(m, 1H), 6.70(s, 1H), 5.96(q, 1H), 5.68(s, 2H), 3.84(d, 2H), 2.68(s, 3H), 1.76(d, 3H)	409 [M + 1]
I-459		N-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-acetamide	2% at 1 uM	as in Example I-14	(400 MHz, CDCl3): d 7.49(s, 1H), 7.29 (m, 1H), 7.06(t, 1H), 6.71(s, 1H), 6.03(q, 1H), 5.49(bs, 1H), 4.82(bs, 2H), 4.29(dd, 1H), 4.12 (dd, 1H), 1.96(s, 3H), 1.83(d, J 8.0 Hz, 3H).	372 [M + 1]

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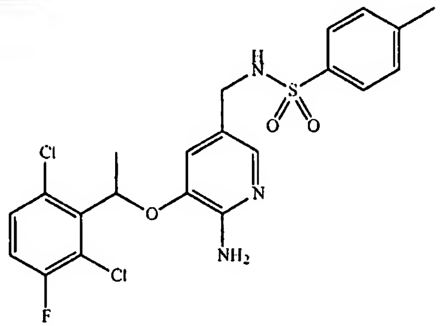
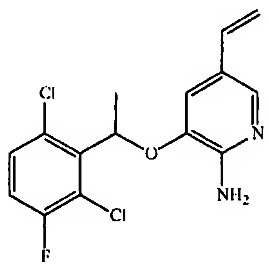
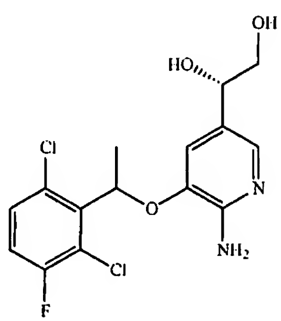
I-460		N-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-ylmethyl}-4-methyl-benzenesulfonamide	9% at 1 uM	as in Example I-13	(400 MHz, CDCl3): d 7.69(d, 2H), 7.29 (m, 4H), 7.06(t, 1H), 6.69(s, 1H), 5.98(q, 1H), 4.84(bs, 2H), 4.51(m, 1H), 3.86(dt, 2H), 2.43(s, 3H), 1.83(d, J 8.0 Hz, 3H).	485 [M + 1]
I-461	 lp;1p	3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine	Ki 0.68	3	(400 MHz, CDCl3): d 7.56(s, 1H), 7.29 (m, 1H), 7.05(t, 1H), 6.91(s, 1H), 6.19(dd, 1H), 6.07(q, 1H), 5.40(d, J 16 Hz, 1H), 5.02(d, J 12 Hz, 1H), 4.85(bs, 2H), 1.85(d, J 8.0 Hz, 3H).	327 [M + 1]
I-462		(S)-1-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-ethane-1,2-diol	2% at 1 uM	Example I-462	(400 MHz, CDCl3): d 7.55(s, 1H), 7.29 (m, 1H), 7.05(t, 1H), 6.82(s, 1H), 6.05(q, 1H), 4.82(bs, 2H), 4.63(m, 1H), 3.54(m, 4H), 1.83(d, J 8.0 Hz, 3H).	362 [M + 1]

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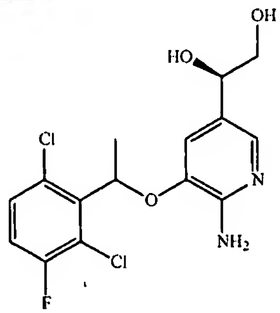
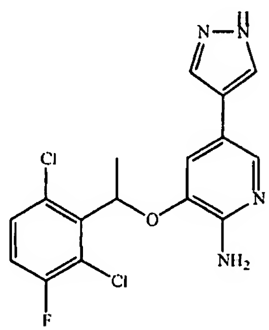
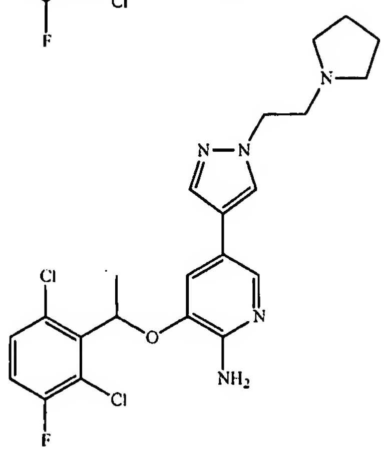
1-463		(R)-1-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-ethane-1,2-diol	2% at 1 uM	as in Example 1-462	(400 MHz, CDCl3): d 7.55(s, 1H), 7.29 (m, 1H), 7.05(t, 1H), 6.82(s, 1H), 6.05(q, 1H), 4.82(bs, 2H), 4.63(m, 1H), 3.54(m, 4H), 1.83(d, J 8.0 Hz, 3H).	362 [M + 1]
1-464		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrazol-4-yl)-pyridin-2-ylamine	Ki 0.10	3	(400 MHz, CDCl3): d 7.65(s, 2H), 7.52 (s, 1H), 7.37(m, 1H), 7.13(m, 1H), 7.04(s, 1H), 6.17(q, J 8.0 Hz, 1H), 1.93(d, J 8.0 Hz, 3H)	367 [M + 1]
1-465		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine	Ki 0.34	14	(400 MHz, CDCl3): d 7.71(s, 1H), 7.55 (s, 2H), 7.37(m, 1H), 7.06(m, 1H), 6.87(s, 1H), 6.09(m, 1H), 4.26(t, J 8.0 Hz, 2H), 2.96(t, J 8.0 Hz, 2H), 2.55(m, 4H), 1.87(d, J 8.0 Hz, 3H), 1.26(m, 4H)	465 [M + 1]

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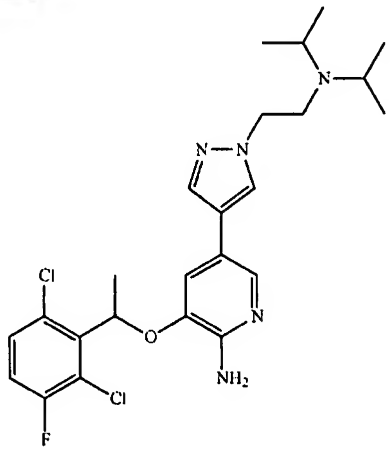
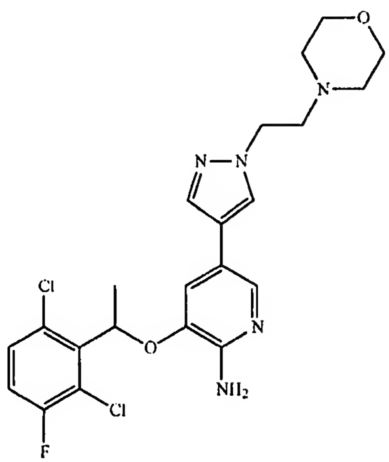
I-466		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-diisopropylamino-ethyl)-1H-pyrazol-4-yl]-pyridin-2-yl amine	Ki 0.47	14	(400 MHz, CDCl3): d 7.76(s, 1H), 7.54 (s, 1H), 7.46(s, 1H), 7.28(m, 1H), 7.04(m, 1H), 6.86(m, 1H), 6.08(m, 1H), 4.05(t, J 8.0 Hz, 2H), 2.83(t, 2H), 1.86(d, J 4.0 Hz, 3H), 0.96(d, J 8.0 Hz, 12H).	495 [M + 1]
I-467		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine	Ki 0.083	14	(400 MHz, CDCl3): d 7.72(s, 1H), 7.60 (s, 1H), 7.50(s, 1H), 7.38(m, 1H), 7.13(m, 1H), 7.05(s, 1H), 6.19(m, 1H), 4.61(m, 2H), 3.89(m, 4H), 3.53(m, 2H), 3.02(m, 4H), 1.93(d, J 8.0 Hz, 3H).	481 [M + 1]

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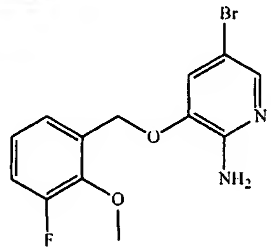
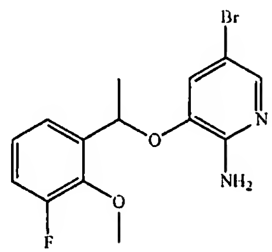
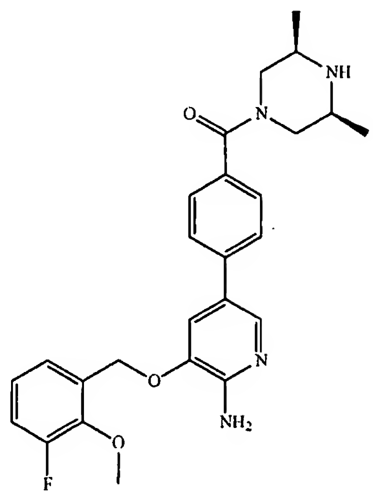
I-468		5-Bromo-3-(3-fluoro-2-methoxy-benzyloxy)-pyridin-2-ylamine	8% at 1 uM	15	(400 MHz, DMSO-d6) δ 7.67(s, 1H), 7.43 (d, 1H), 7.40(d, 1H), 7.33(t, 1H), 7.20(m, 1H), 6.00(s, 2H), 5.19(s, 2H), 3.96(s, 3H)	328 [M + 1]
I-469		5-Bromo-3-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-2-ylamine	7% at 1 uM	15	(400 MHz, DMSO-d6) δ 7.51(s, 1H), 7.25 (d, 1H), 7.18(m, 1H), 7.09(m, 1H), 6.94(s, 1H), 6.02(s, 2H), 5.72(q, 1H), 3.93(s, 3H), 1.57(d, 3H)	342 [M + 1]
I-470		{4-[6-Amino-5-(3-fluoro-2-methoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	3% at 1 uM	3	(400 MHz, DMSO-d6) δ 9.24(s, 1H), 8.61 (d, 1H), 7.96(d, 1H), 7.81(d, 2H), 7.57(d, 1H), 7.43(d, 2H), 7.32(t, 1H), 7.18(m, 1H), 5.34(s, 2H), 3.91(s, 3H), 3.39(m, 2H), 2.49(m, 4H), 1.21(m, 6H).	465 [M + 1]

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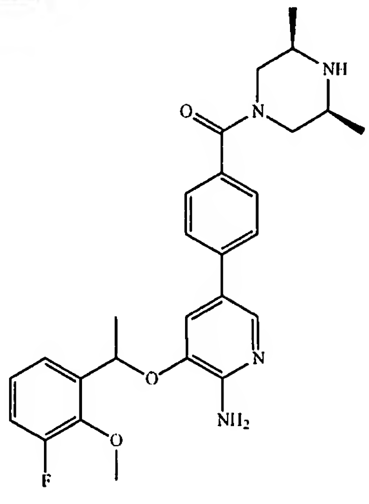
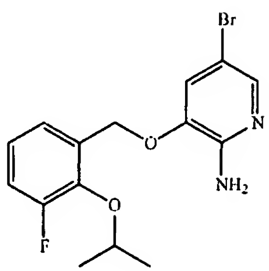
I-471		(4-{6-Amino-5-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	1% at 1 μM	3	(400 MHz, DMSO-d6) δ 9.25(d, 1H), 8.64 (d, 1H), 7.88(s, 1H), 7.61(d, 2H), 7.53(d, 2H), 7.46(s, 1H), 7.35(d, 1H), 7.21(s, 1H), 7.13(m, 1H), 6.03(m, 1H), 3.93(s, 3H), 3.38(m, 2H), 2.49(m, 4H), 1.67(d, 3H), 1.20(m, 6H)	479 [M + 1]
I-472		5-Bromo-3-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-2-ylamine	Ki 12.1	15	(400 MHz, DMSO-d6) δ 7.59(s, 1H), 7.36 (d, 1H), 7.31(d, 1H), 7.25(t, 1H), 7.12 (m, 1H), 5.90(s, 2H), 5.10(s, 2H), 4.43(m, 1H), 1.26(d, 6H)	356

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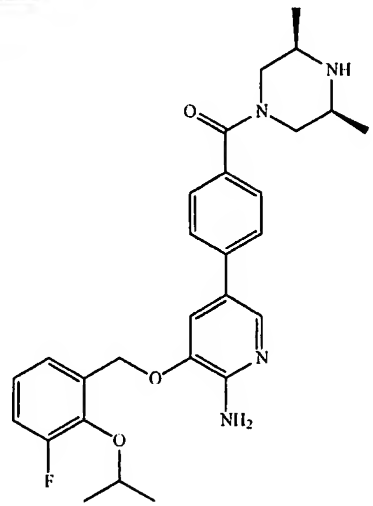
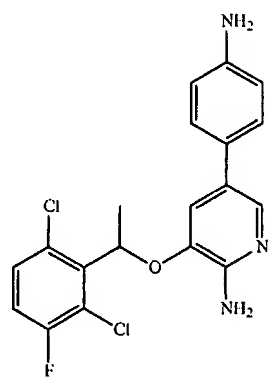
I-473		{4-[6-Amino-5-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	Ki 12.7	3	(400 MHz, DMSO-d6) δ 9.45(d, 1H), 8.79 (q, 1H), 7.99(s, 1H), 7.88(s, 1H), 7.80 (d, 2H), 7.58(d, 2H), 7.41(d, 1H), 7.32(t, 1H), 7.17(m, 1H), 5.37(s, 2H), 4.45(m, 1H), 3.40(m, 2H), 2.49(m, 4H), 1.28(d, 8H), 1.20(m, 6H)	493
I-474		5-(4-Amino-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		3	(400 MHz, DMSO-d6) δ 7.66(d, 1H), 7.55 (q, 1H), 7.43(t, 1H), 7.02(d, 2H), 6.81 (s, 1H), 6.56(d, 2H), 6.08(q, 1H), 5.60(s, 2H), 5.08(s, 2H), 1.78(d, 3H)	393

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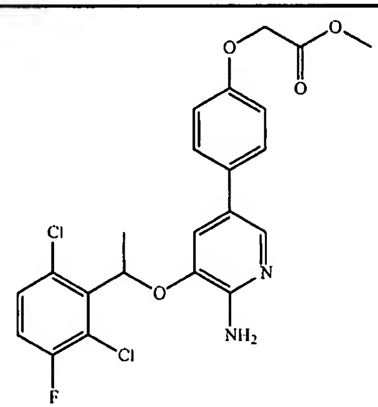
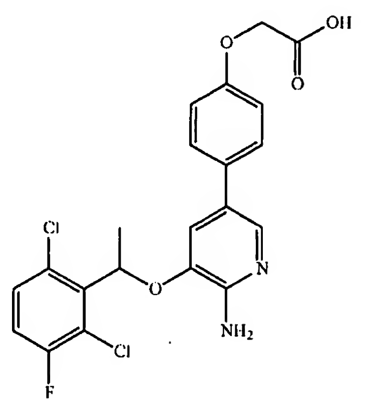
I-475		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid methyl ester	Ki 0.20	as in Example I-55	(400 MHz, CDCl3): d 7.82(s, 1H), 7.30 (m, 3H), 7.06(m, 1H), 6.95(m, 3H), 6.12 (q, 1H), 4.80(m, 2H), 4.66(s, 2H), 3.82(s, 3H), 1.86(d, J 8.0 Hz, 3H).	467
I-476		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid	Ki 0.20	as in Example I-55	(400 MHz, CDCl3): d 7.70(s, 1H), 7.50 (m, 2H), 7.45(m, 2H), 7.20(m, 2H), 6.85 (m, 2H), 6.05(q, 1H), 5.72(s, 2H), 4.49(s, 2H), 3.82(s, 3H), 1.75 (d, J 8.0 Hz, 3H).	453

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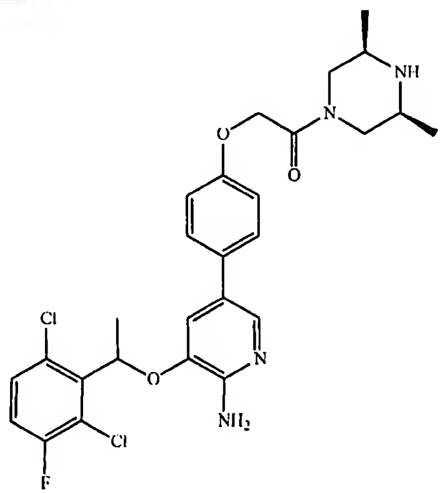
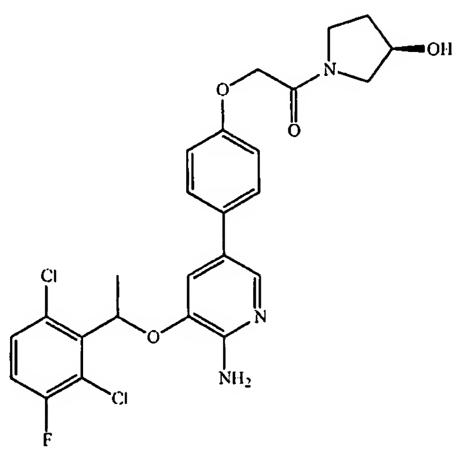
I-477		2-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-ethanone	Ki 0.027	4	(400 MHz, CDCl3): d 7.48(s, 1H), 7.35 (m, 1H), 7.20(m, 2H), 7.12 (m, 2H), 7.01 (m, 2H), 6.20(q, 1H), 4.73(m, 3H), 4.10(m, 1H), 3.36(m, 1H), 3.13 (m, 2H), 2.84(m, 1H), 1.94(d, J 8.0 Hz, 3H), 1.34(m, 6H).	548
I-478		2-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-3-hydroxy-pyrrolidin-1-yl)-ethanone	Ki 0.041	4	(400 MHz, CDCl3): d 7.48(s, 1H), 7.36 (m, 1H), 7.21(d, 2H), 7.19(m, 2H), 7.10 (m, 2H), 7.01(m, 2H), 6.20(q, 1H), 4.65(m, 2H), 4.55(m, 1H), 3.69 (m, 3H), 3.48(m, 1H), 2.10(m, 3H), 1.92 (m, 5H).	521

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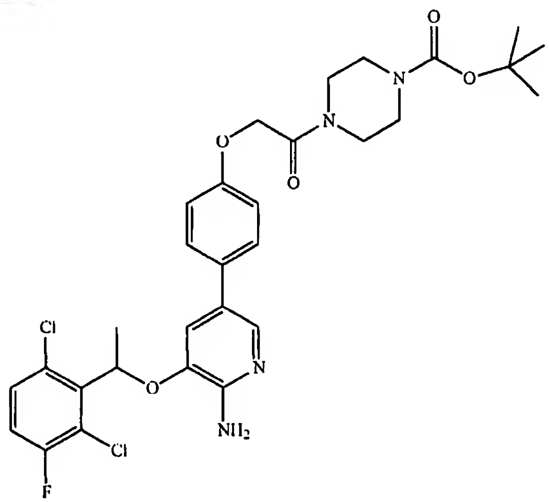
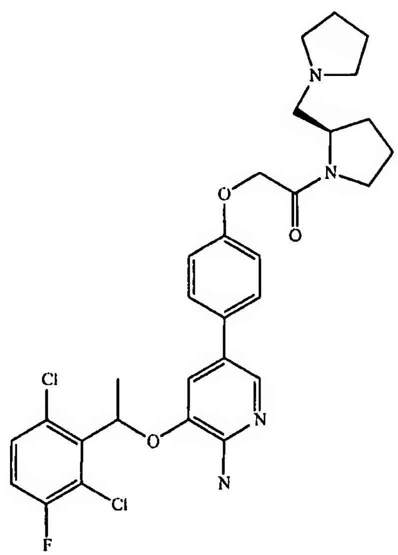
I-479		4-[2-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester	Ki 0.16	4	(400 MHz, CDCl3): d 7.50(s, 1H), 7.36 (m, 1H), 7.22(d, 2H), 7.19(m, 2H), 7.15 (m, 2H), 7.00(m, 2H), 6.20(q, 1H), 4.75(s, 2H), 3.57(m, 4H), 3.45 (m, 4H), 1.93(d, J 8.0 Hz, 3H), 1.47 (s, 9H).	620
I-480		2-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-ethanone		4	(400 MHz, CDCl3): d 7.48(s, 1H), 7.36 (m, 1H), 7.20(d, 2H), 7.15(m, 2H), 7.00 (d, 2H), 6.20(q, 1H), 4.68(s, 2H), 4.46(m, 1H), 4.04(m, 1H), 3.93 (m, 1H), 3.60(m, 1H), 3.52(m, 1H), 3.50(m, 1H), 3.12 (m, 1H), 3.09(m, 1H), 2.83(m, 1H), 1.93(d, J 8.0 Hz, 3H), 2.16–1.66(m, 10H).	588

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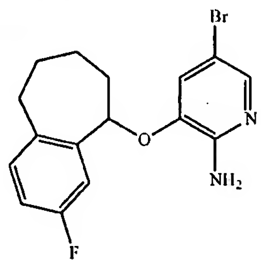
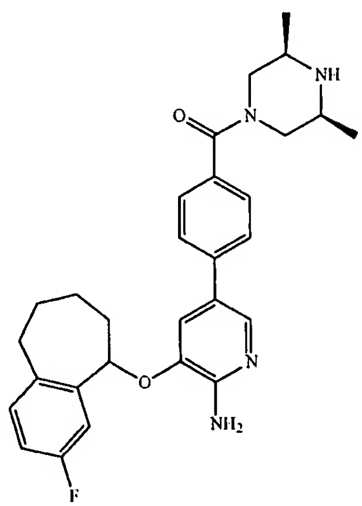
I-481		5-Bromo-3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-2-ylamine	15	(400 MHz, DMSO-d6) δ 7.57(d, 1H), 7.16 (m, 3H), 6.95(dt, 1H), 6.07(d, 2H), 5.63(d, 1H), 2.10(m, 2H), 2.16(m, 2H), 1.86 (m, 1H), 1.77(m, 2H), 1.34(m, 1H).	352
I-482		{4-[6-Amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	3		493

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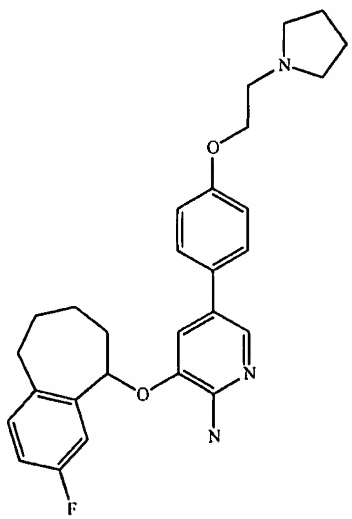
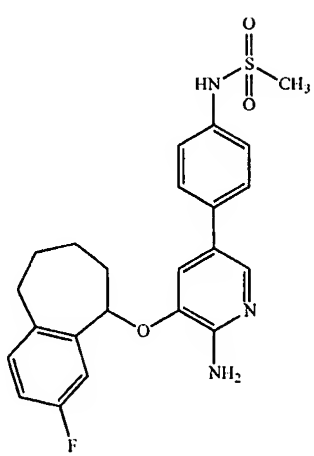
I-483		3-(3-Fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-[4-(2-pyrralidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine	3	462
I-484		N-{4-[6-Amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide	3	442

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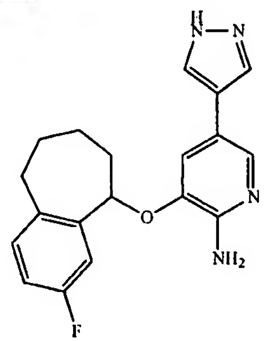
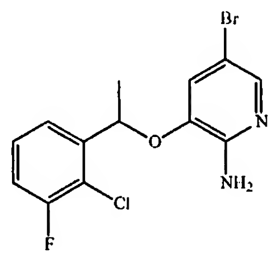
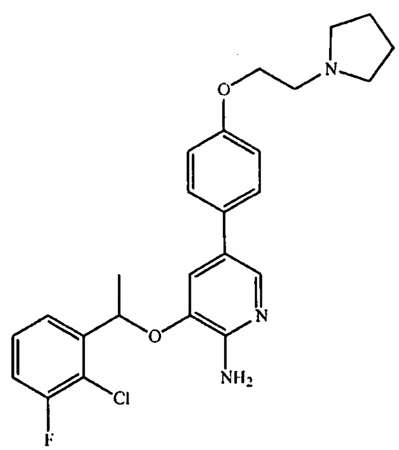
I-485		3-(3-Fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-(1H-pyrazol-4-yl)-pyridin-3-ylamine		3		337 [M − 1]
I-486		5-Bromo-3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine	0% at 1 uM	15	(400 MHz, CDCl3): d 7.68(s, 1H), 7.24(m, 3H), 6.69(s, 1H), 5.64(q, 1H), 4.78(bs, 2H), 1.68(d, J 8.0 Hz, 3H).	347
I-487		3-[1-(2-Chloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine	Ki 3.30	3	(400 MHz, CDCl3): d 7.50(s, 1H), 7.30(m, 2H), 7.20(m, 3H), 7.00(s, 1H), 6.95(m, 2H), 5.90(q, 1H), 4.36(m, 2H), 3.85(m, 2H), 3.55(m, 2H), 2.95(m, 2H), 2.10(m, 4H), 1.82(d, J 8.0 Hz, 3H).	456

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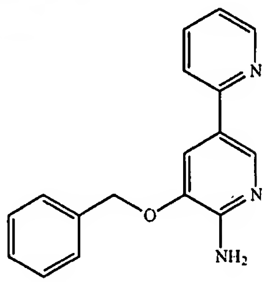
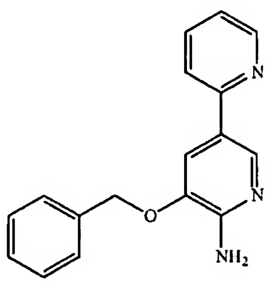
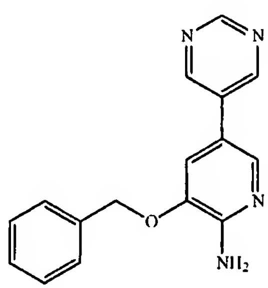
I-488		5'-Benzyloxy-[2,3'] bipyridinyl-6'-ylamine	>20	16	(CDCl3) d 5.15(br s, 2H), 5.19(s, 2H), 7.17(m, 1H), 7.34–7.46(m, 5H), 7.64(d, J=8 Hz, 1H), 7.70(td, J=7.8, 1.9 Hz, 1H), 7.86(d, J=1.6 Hz, 1H), 8.22(d, J=2 Hz, 1H), 8.63(d, J=4 Hz, 1H).	278
I-489		5-Benzyloxy-[3,3'] bipyridinyl-6-ylamine	>20	16	(CDCl3) d 5.17(s, 2H), 5.27(br s, 2H), 7.19(d, J=2 Hz, 1H), 7.33(dd, J=7.8, 4.6 Hz, 1H), 7.35–7.44(m, 5H, 7.70(dt, J=2, 8 Hz, 1H), 7.85(d, J=2 Hz, 1H), 8.56 (dd, J=1.6, 4.8 Hz, 1H), 8.71 (d, J=2Hz, 1H).	278
I-490		3-Benzyloxy-5-pyrimidin-5-yl-pyridin-2-ylamine	>20	16	(CDCl3) d 5.22(s, 2H). 6.15(brs, 2H), 7.21(s, 1H), 7.43(m, 5H), 7.77(s, 1H), 8.81(s, 2H), 9.20(s, 1H).	279

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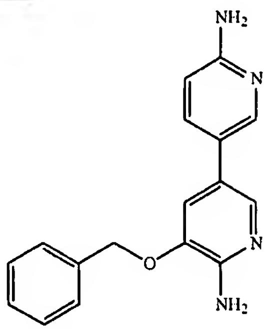
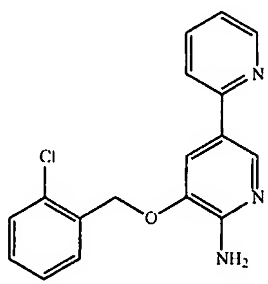
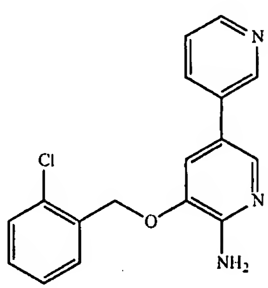
I-491		5-Benzyloxy-[3,3']bipyridinyl-6,6'-diamine	>20	16	(CDCl3) d 4.40(br s, 2H), 4.94(br s, 2H), 5.13(s, 2H), 6.58(d, J=8.4 Hz, 1H), 7.09(d, J=1.6 Hz, 1H), 7.35-7.44(m, 5H), 7.56(dd, J=2.4, 8.4 Hz, 1H), 7.77(d, J=1.6 Hz, 1H), 8.13(d, J=2 Hz, 1H).	293
I-492		5'-(2-Chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine	8.24	16	(CDCl3) d 5.33(s, 2H), 5.99(bs, 2H), 7.22-7.26(m, 1H), 7.29-7.37(m, 2H), 7.42-7.51(m, 2H), 7.63(d, 1H), 7.72(dt, 1H), 7.99(d, 1H), 8.13(d, 1H), 8.65 (dd, 1H).	312
I-493		5-(2-Chloro-benzyloxy)-[3,3'[bipyridinyl-6-ylamine	4.6	16		312

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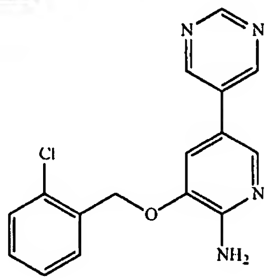
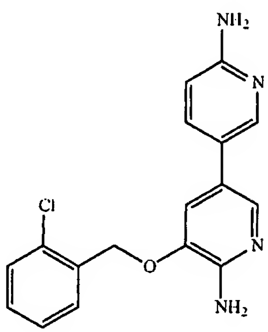
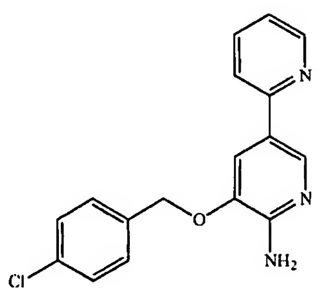
I-494		3-(2-Chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine	19.3	16		313
I-495		5-(2-Chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine	4.31	16		317
I-496		5'-(4-Chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine	14	16	(CDCl3) d 5.18(s, 2H), 5.48(bs, 2H), 7.19–7.22(m, 1H), 7.38(s, 4H), 7.63–7.65(m, 1H), 7.73(dt, 1H), 7.89(d, 1H), 8.17(d, 1H), 8.63(d, 1H).	312

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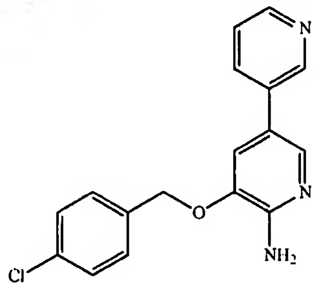
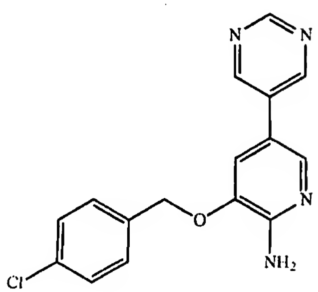
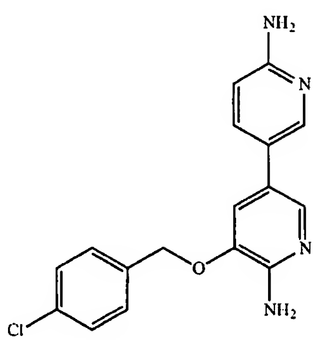
I-497		5-(4-Chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine	14.1	16	312
I-498		3-(4-Chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine	>20.0	16	313
I-499		5-(4-Chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine	>20.0	16	317

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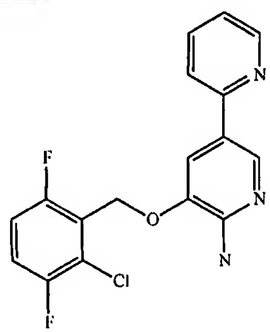
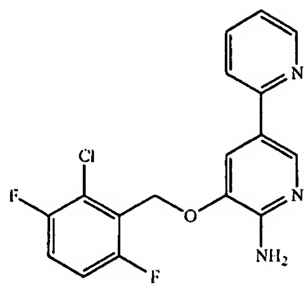
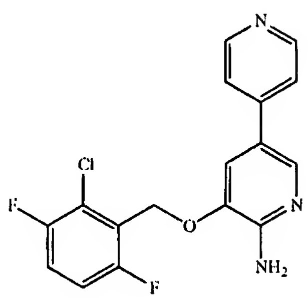
I-500		5'-(2-Chloro-3,6-difluoro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine	1.8	16	(CDCl3) δ 5.39(s, 2H), 6.19(bs, 2H), 7.08 (dt, 1H), 7.21-7.28(m, 2H), 7.65(d, 1H), 7.77(dt, 1H), 8.13(d, 1H), 8.67(dd, 1H)	348
I-501		5-(2-Chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6-ylamine	0.282	16		348
I-502		5-(2-Chloro-3,6-difluoro-benzyloxy)-[3,4']bipyridinyl-6-ylamine	0.211	16		348

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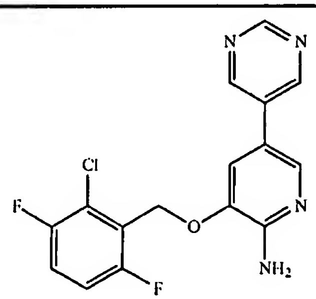
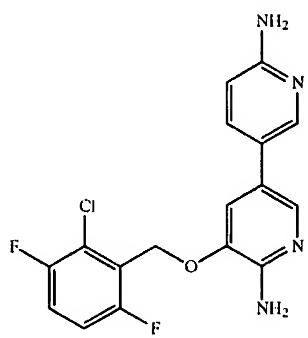
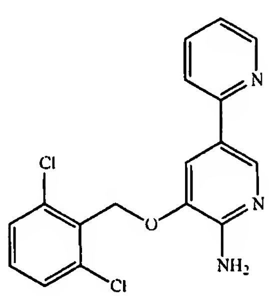
I-503		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine	2.15	16		349
I-504		5-(2-Chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine	0.209	16		363
I-505		5'-(2,6-Dichloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine	2.84	16	(CDCl3) d 5.47(s, 2H), 5.76(bs, 2H), 7.21–7.25(m, 1H), 7.27–7.32(m, 1H), 7.37–7.41(m, 2H), 7.66(d, 1H), 7.75(dt, 1H), 8.06(d, 1H), 8.17(d, 1H), 8.66 (dd, 1H).	346

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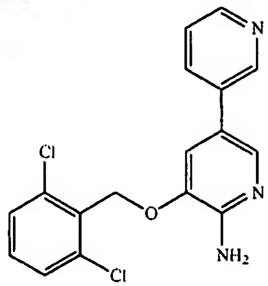
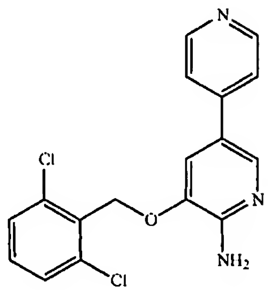
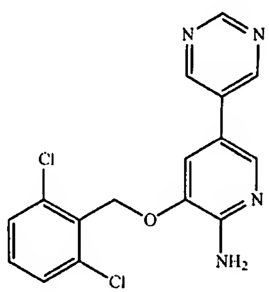
I-506		5-(2,6-Dichloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine	2.71	16	346
I-507		5-(2,6-Dichloro-benzyloxy)-[3,4']bipyridinyl-6-ylamine	1.3	16	346
I-508		3-(2,6-Dichloro-benzyloxy)-pyrimidin-5-yl-pyridin-2-ylamine	10.3	16	347

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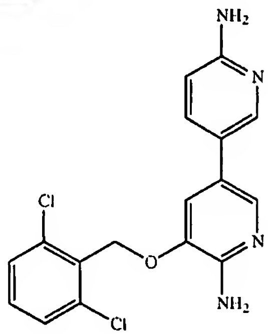
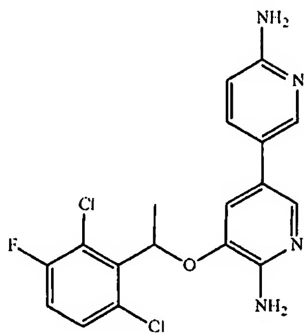
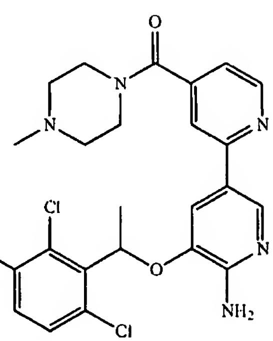
I-509		5-(2,6-Dichloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine	0.578	16		361
I-510		5-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine	0.0167	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 4.60 (br s, 2H), 4.96(br s, 2H), 6.11(q, J=6.6 Hz, 1H), 6.56(d, J=8.4 Hz, 1H), 6.91 (s, 1H), 7.06(t, J=8.5 Hz, 1H), 7.31(dd, J=4.8, 8.7 Hz, 1H), 7.48(dd, J=1.8, 8.4 Hz, 1H), 7.75(s, 1H), 8.05(s, 1H).	393
I-511		{6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0742	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 2.37 (s, 3H), 2.39(br s, 2H), 2.56(br s, 2H), 3.43(br s, 2H), 3.86(br s, 2H), 5.13 (br s, 2H), 6.21(q, J=6.7 Hz, 1H), 7.04 (dd, J=8.1, 8.7 Hz, 1H), 7.10(dd, J=1.2, 5.1 Hz, 1H), 7.29(dd, J=5.1, 9.3 Hz, 1H), 7.48(s, 1H), 7.57(d, J=1.5 Hz, 1H), 8.24(d, J=1.8 Hz, 1H), 8.65(dd, J=0.6, 4.8 Hz, 1H).	504

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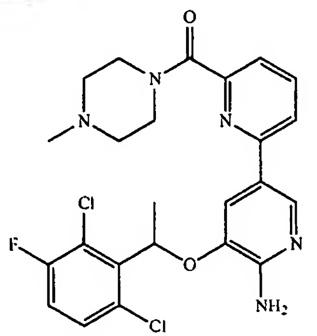
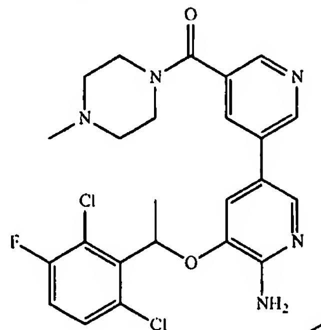
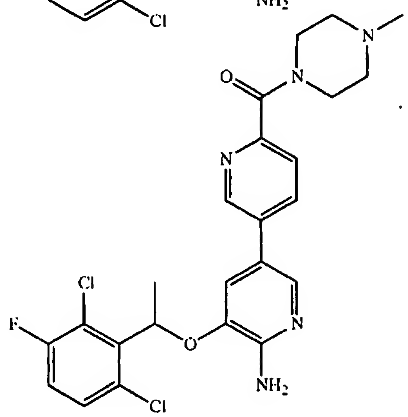
I-512		{6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0629	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 2.36 (s, 3H), 2.46(m, 2H), 2.58(m, 2H), 3.66 (m, 2H), 3.89(m, 2H), 5.08(br s, 2H), 6.17(q, J=6.6 Hz, 1H), 7.05(dd, J=8.1, 8.8 Hz, 1H), 7.31(dd, J=5.0, 8.9 Hz, 1H), 7.46(dd, J=0.8, 7.7 Hz, 1H), 7.51(d, J=1.8 Hz, 1H), 7.55(dd, J=0.8, 8.0 Hz, 1H), 7.76(t, J=7.5 Hz, 1H), 8.27(d, J=1.2 Hz, 1H).	504
I-513		{6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone	0.034	16	(CDCl3) d 1.88(d, J=6.6 Hz, 3H), 2.38 (s, 3H), 2.44(m, 2H), 2.56(m, 2H), 3.52 (m, 2H), 3.87(m, 2H), 5.05(br s, 2H), 6.12 (q, J=6.7 Hz, 1H), 6.97(d, J=1.8 Hz, 1H), 7.08(dd, J=8.1, 8.7 Hz, 1H), 7.33(dd, J=5.0, 8.9 Hz, 1H), 7.72 (t, J=2.1 Hz, 1H), 7.86(d, J=2.1 Hz, 1H), 8.54(d, J=1.8 Hz, 1H), 8.65(d, J=2.4 Hz, 1H).	504
I-514		{6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0213	16	(CDCl3) d 1.88(d, J=6.9 Hz, 3H), 2.39 (s, 3H), 2.52(br s, 2H), 2.61(br s, 2H), 3.74(br s, 2H), 3.89(br s, 2H), 5.02(br s, 2H), 6.12 (q, J=6.7 Hz, 1H), 6.97(d, J=1.2 Hz, 1H), 7.08(t, J=8.4 Hz, 1H), 7.33 (dd, J=4.8, 8.7 Hz, 1H), 7.68(d, J=9 Hz, 1H), 7.76(dd, J=1.8, 8.4 Hz, 1H), 7.89(d, J=1.5 Hz, 1H), 8.59(d, J=1.5 Hz, 1H).	504

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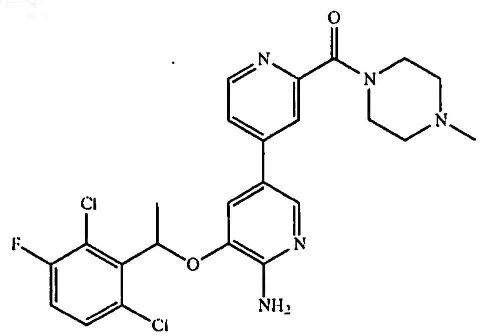
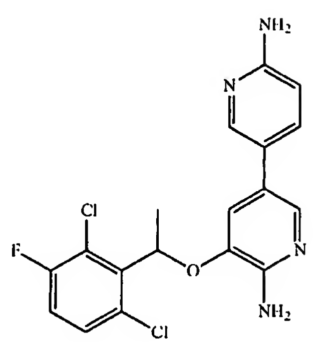
I-515		{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0387	16	(CDCl3) d 1.88(d, J=6.9 Hz, 3H), 2.39 (s, 3H), 2.51(m, 2H), 2.61(m, 2H), 3.67 (m, 2H), 3.90(m, 2H), 5.08(br s, 2H), 6.14 (q, J=6.7 Hz, 1H), 7.05(s, 1H), 7.06(dd, J=7.8, 9 Hz, 1H), 7.32(d, J=5.1 Hz, 1H), 7.34(dd, J=5.0, 7.7 Hz, 1H), 7.66 (d, J=1.2 Hz, 1H), 8.00 (d, J=1.8 Hz, 1H), 8.53(d, J=5.1 Hz, 1H).	504
I-516		5-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine	0.0393	16	(CDCl3) d 1.83(d, J=6.6 Hz, 3H), 4.55 (br s, 2H), 4.87(br s, 2H), 5.95(q, J=6.5 Hz, 1H), 6.55(d, S =8.4 Hz, 1H), 6.93–7.12 (m, 3H), 7.48(dd, J=1.8, 8.4 Hz, 1H), 7.76(s, 1H), 8.09(s, 1H).	377

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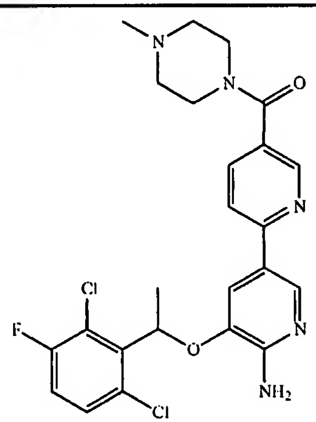
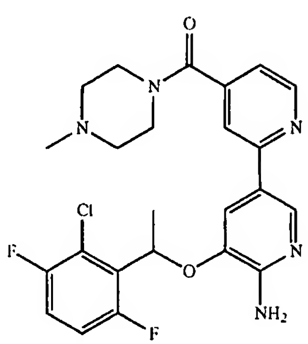
I-517		{6'-Amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone	0.131	16	(CDCl3) d 1.84(d, J=6.6 Hz, 3H), 2.39 (s, 3H), 2.53(br s, 4H), 3.63(br s, 2H), 3.82(br s, 2H), 5.09(br s, 2H), 6.06(q, J=6.5 Hz, 1H), 6.93–7.10(m, 2H), 7.60(d, J=7.8 Hz, 1H), 7.69(d, J=7.8 Hz, 1H), 7.76(dd, J=2.1, 8.4 Hz, 1H), 8.28 (d, J=1.5 Hz, 1H), 8.66(d, J=1.5 Hz, 1H).	488
I-518		{6'-Amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone	0.209	16	(CDCl3) d 1.84(d, J=6.6 Hz, 3H), 2.40 (s, 3H), 2.45(br s, 2H), 2.61(br s, 2H), 3.48(br s, 2H), 3.89(br s, 2H), 5.13(br s, 2H), 6.06(q, J=6.6 Hz, 1H), 6.93–7.10(m, 2H), 7.12 (dd, J=1.2, 5.1 Hz, 1H), 7.52(s, 1H), 7.68(d, J=1.2 Hz, 1H), 8.24(d, J=1.8 Hz, 1H), 8.67(d, J=4.8 Hz, 1H).	488

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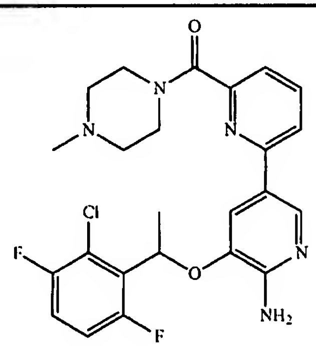
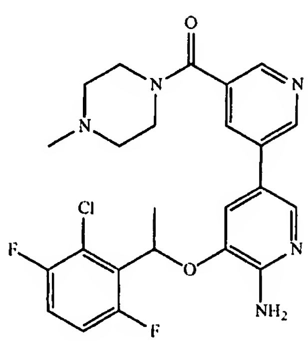
I-519		{6'-Amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone	0.466	16	(CDCl3) d 1.84(d, J=6.6 Hz, 3H), 2.38 (s, 3H), 2.49(m, 2H), 2.60(m, 2H), 3.70 (m, 2H), 3.91(m, 2H), 5.01(br s, 2H), 6.02 (q, J=6.6 Hz, 1H), 6.93–7.12 (m, 2H), 7.49(dd, J=0.8, 7.7 Hz, 1H), 7.58(dd, J=0.9, 8:1 Hz, 1H), 7.62(d, J=1.8 Hz, 1H), 7.78(t, J=7.8 Hz, 1H), 8.29(d, J=1.8 Hz, 1H).	488
I-520		{6'-Amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone	0.134	16	(CDCl3) d 1.85(d, J=6.6 Hz, 3H), 2.44 (s, 3H), 2.57(m, 4H), 3.59(m, 2H), 3.91 (m, 2H), 5.02(br s, 2H), 5.97(q, J=6.4 Hz, 1H), 6.96–7.14(m, 3H), 7.74(s, 1H), 7.87 (br s, 1H), 8.57(br s, 1H), 8.71(br s, 1H).	488

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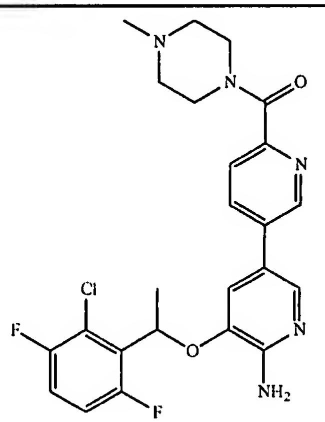
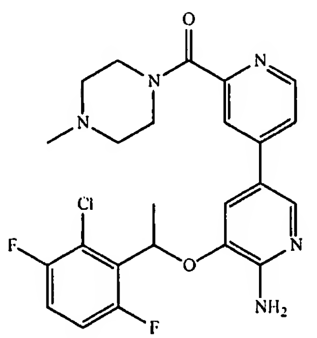
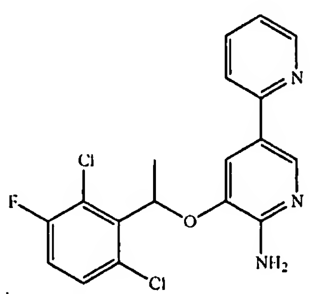
I-521		{6'-Amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0716	16	(CDCl3) d 1.86(d, J=6.6 Hz, 3H), 2.45 (s, 3H), 2.62(br s, 2H), 2.69(br s, 2H), 3.82(br s, 2H), 3.95(br s, 2H), 4.97(br s, 2H), 5.98(q, J=6.5 Hz, 1H), 6.96–7.14(m, 3H), 7.71(d, J=8.1 Hz, 1H), 7.79(dd, J=2.3, 8.3 Hz, 1H), 7.90(d, J=2.1 Hz, 1H), 8.62(d, J=1.5 Hz, 1H).	488
I-522		{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone	0.0626	16	(CDCl3) d 1.86(d, J=6.6 Hz, 3H), 2.45 (s, 3H), 2.62(br s, 2H), 2.70(br s, 2H), 3.77(br s, 2H), 3.96(br s, 2H), 5.03(br s, 2H), 5.99(q, J=6.7 Hz, 1H), 6.96–7.14(m, 2H), 7.16(d, J=1.8 Hz, 1H), 7.36(dd, J=2.0, 5.3 Hz, 1H), 7.71(d, J=1.2 Hz, 1H), 8.01(d, J=1.8 Hz, 1H), 8.45(d, J=4.8 Hz, 1H).	488
I-523		5'-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine	0.0677	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 5.20 (br s, 2H), 6.23(q, J=6.7 Hz, 1H), 7.04 (t, J=8.4 Hz, 1H), 7.15(dd, J=4.8, 6.6 Hz, 1H), 7.29(dd, J=5.1, 9.3 Hz, 1H), 7.51(d, J=8.1 Hz, 1H), 7.59(d, J=1.2 Hz, 1H), 7.67(td, J=7.8, 1.8 Hz, 1H), 8.24(d, J=1.5 Hz, 1H), 8.60(d, J=3.9 Hz, 1H).	378

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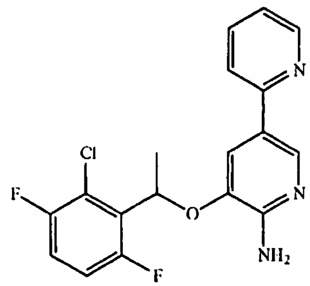
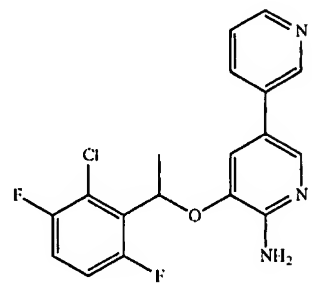
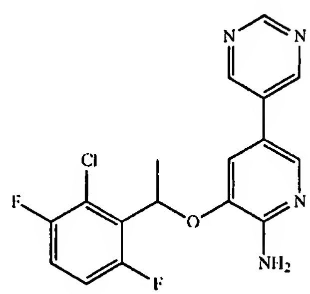
I-524		5'-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine	0.612	16	(CDCl3) d 1.84(d, J=6.9 Hz, 3H), 5.14 (br s, 2H), 6.08(q, J=6.5 Hz, 1H), 6.93-7.10(m, 2H), 7.16(dd, J=5.1, 6.6 Hz, 1H), 7.54(d, J=8.1 Hz, 1H), 7.65-7.70(m, 2H), 8.24(s, 1H), 8.62(d, J=4.2 Hz, 1H)	362
I-525		5-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine	0.0777	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 5.37 (br s, 2H), 6.00(q, J=6.5 Hz, 1H), 6.97-7.15(m, 3H), 7.34(dd, J=4.7, 7.7 Hz, 1H), 7.69(d, J=7.8 Hz, 1H), 7.82(s, 1H), 8.56(d, J=3.9 Hz, 1H), 8.65(s, 1H).	362
I-526		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-pyrimidin-5-yl-pyridin-2-ylamine	0.552	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 5.16 (br s, 2H), 5.98(q, J=6.5 Hz, 1H), 6.96-7.14(m, 3H), 7.86(s, 1H), 8.77(s, 2H), 9.14(s, 1H).	363

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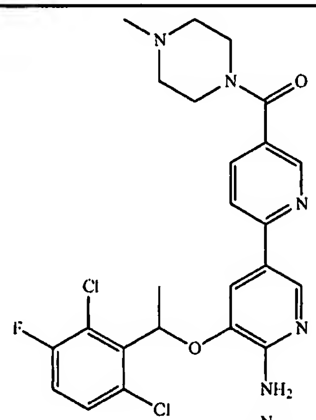
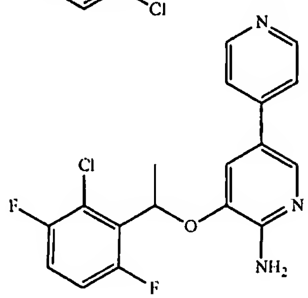
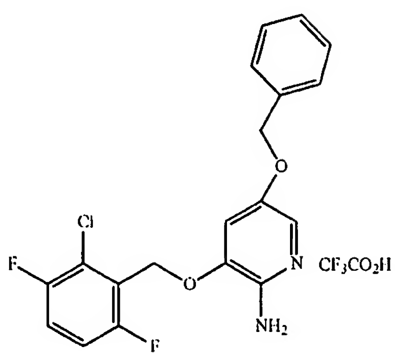
I-527		{6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}(4-methyl-piperazin-1-yl)-methanone	0.0385	16	(CDCl3) d 1.87(d, J=6.6 Hz, 3H), 2.38 (s, 3H), 2.51(brs, 4H), 3.62(br s, 2H), 3.81 (br s, 2H), 5.13(br s, 2H), 6.21(q, J=6.7 Hz, 1H), 7.04(t, J=8.4 Hz, 1H), 7.30 (dd, J=4.8, 8.7 Hz, 1H), 7.75(dd, J=1.9, 8.2 Hz, 1H), 8.28(s, 1H), 8.64(s, 1H).	504
I-528		5-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-6-ylamine	0.0659	16	(CDCl3) d 1.84(d, J=6 Hz, 3H), 5.13(br s, 2H), 5.97(q, J=6.5 Hz, 1H), 6.95–7.10 (m, 2H), 7.12 (d, J=1.6 Hz, 1H), 7.30(d, J=6 Hz, 2H), 7.95(d, J=2 Hz, 1H), 8.58(d, J=5.6 Hz, 2H).	362
I-529		5-Benzyloxy-3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-2-ylamine	2.58	17	(CDCl3) d 1.84(d, 3H), 4.88(s, 2H), 5.89(q, 1H), 6.79(d, 1H), 6. + 1(d, 1H), 7.01 (dt, 1H), 7.11–7.17(m, 1H), 7.28–7.40(m, 5H).	391

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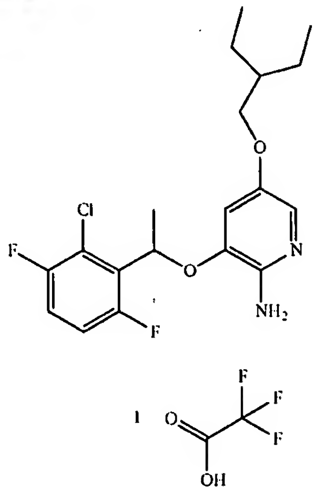
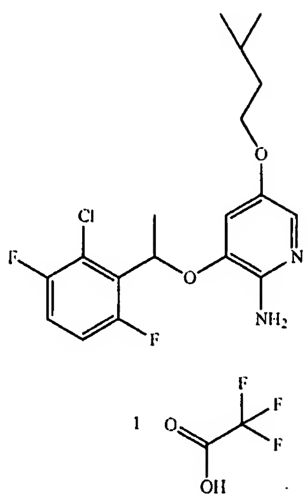
I-530		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-ethyl-butoxy)-pyridin-2-ylamine	4.08	17	385
I-531		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-(3-methyl-butoxy)-pyridin-2-ylamine	2.4	17	371

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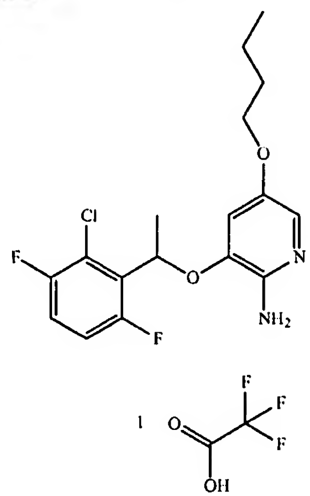
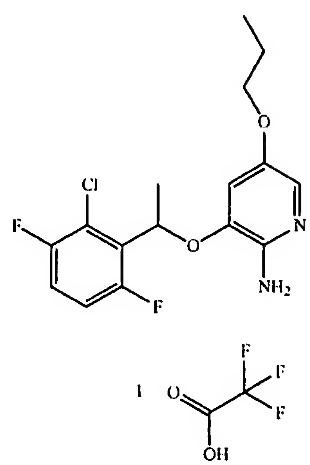
I-532		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-butoxy-pyridin-2-ylamine	1.94	17	357
I-533		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-propoxy-pyridin-2-ylamine	0.672	17	343

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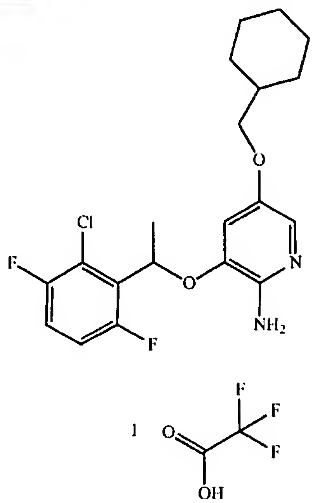
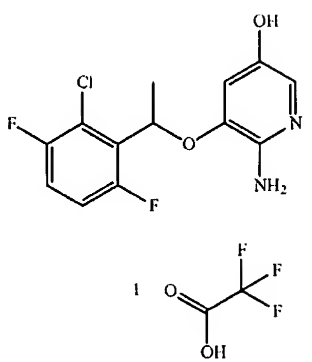
I-534		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-cyclohexylmethoxy-pyridin-2-ylamine	5.97	17	397
I-535		6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-ol	0.54	17	301

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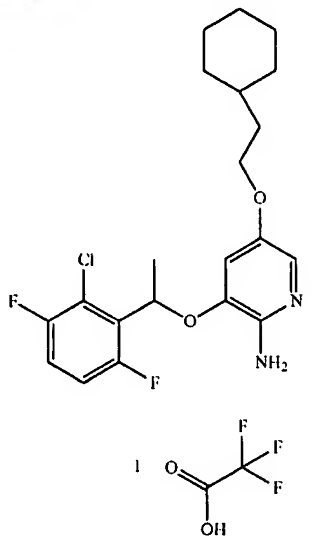
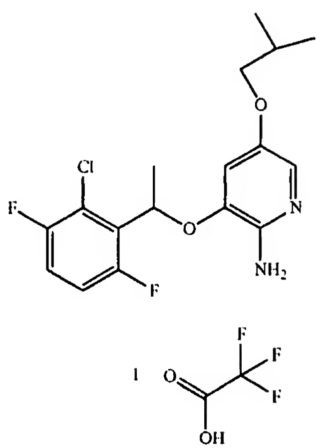
I-536		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-(2-cyclohexyl-ethoxy)-pyridin-2-ylamine	7.5	17	411
I-537		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-isobutoxy-pyridin-2-ylamine	1.2	17	357

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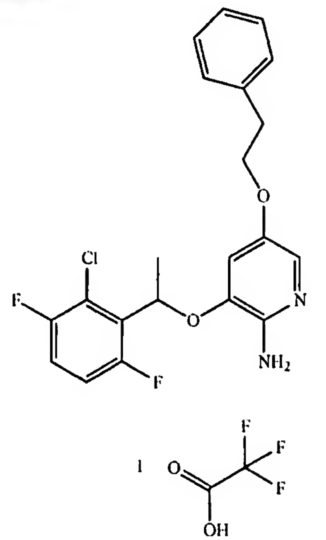
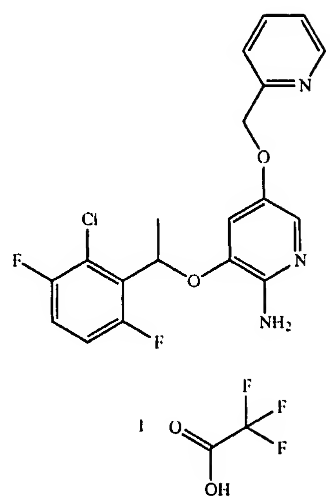
I-538		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-phenethyloxy-pyridin-2-ylamine	2.8	17	405
I-539		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-2-ylmethoxy)-pyridin-2-ylamine	3.2	17	392

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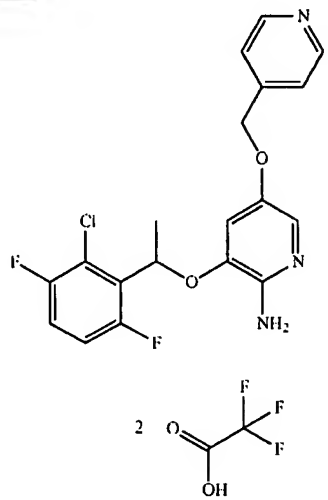
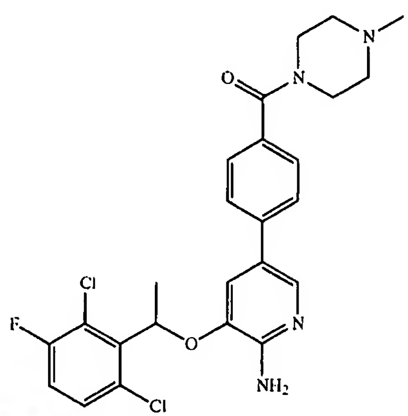
I-540		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-(pyridin-4-ylmethoxy)-pyridin-2-ylamine	0.8	17		392
I-541		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.079	4 as in Example I-291	(300 MHz, CDCl3) δ 7.89(s, 1H), 7.40 (m, 4H), 7.35(dd, 1H), 7.08(t, 1H), 7.02(s, 1H), 6.17(q, 1H), 4.98(s, 2H), 3.82(m, 2H), 3.62(m, 2H), 2.52(m, 4H), 1.88(d, 3H).	567

TABLE 3

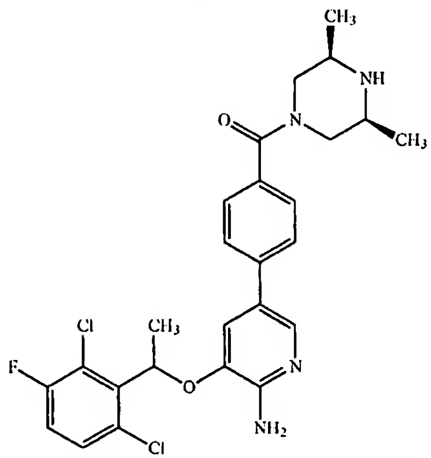
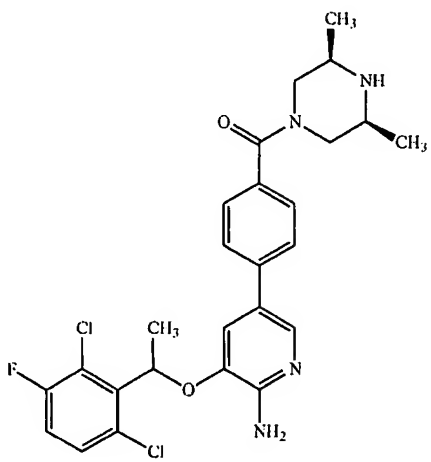
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-542		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.023	(400 MHz, DMSO-D6) d ppm 0.84(s, 3H) 0.93–1.10(m, 3H) 1.80(d, J=6.57 Hz, 3H) 2.30(s, 2H) 2.55–2.74(m, 2H) 3.38–3.49(m, 1H) 4.32 (s, 1H) 5.96(s, 2H) 6.14(q, J=6.57 Hz, 1H) 7.00(d, J=1.77 Hz, 1H) 7.36(m, 2H) 7.45(m, 3H) 7.56(dd, J=8.97, 4.93 Hz, 1H) 7.88(d, J=1.77 Hz, 1H)	517	18/19/20/31
I-543		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	1.5	(400 MHz, DMSO-D6) d ppm 0.84(s, 3H) 0.93–1.10(m, 3H) 1.80(d, J=6.57 Hz, 3H) 2.30(s, 2H) 2.55–2.74(m, 2H) 3.38–3.49(m, 1H) 4.32 (s, 1H) 5.96(s, 2H) 6.14(q, J=6.57 Hz, 1H) 7.00(d, J=1.77 Hz, 1H) 7.36(m, 2H) 7.45(m, 3H) 7.56(dd, J=8.97, 4.93 Hz, 1H) 7.88(d, J=1.77 Hz, 1H)	517	18/19/20/31

TABLE 3-continued

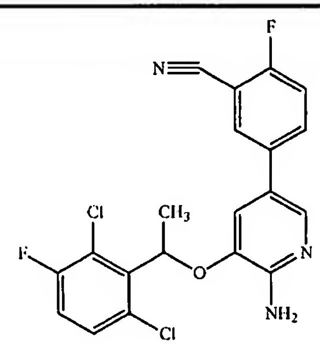
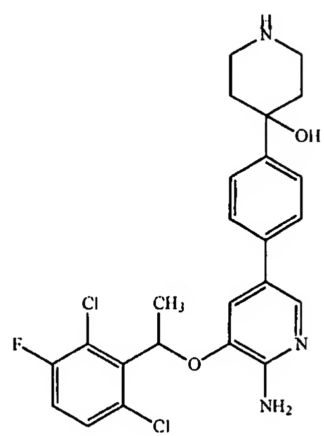
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-544		5-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-benzonitrile		(400 MHz, DMSO-D6) d ppm 1.80(d, J=6.82 Hz, 3H) 6.01(s, 2H) 6.17(q, J=6.57 Hz, 1H) 7.05 (d, J=1.77 Hz, 1H) 7.44(t, J=8.72 Hz, 1H) 7.55 (m, 2H) 7.79(m, 1H) 7.89(d, J=1.77 Hz, 1H) 7.97(dd, J=6.06, 2.27 Hz, 1H)	420	27
I-545		4-(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxyl]-pyridin-3-yl}-phenyl)-piperidin-4-ol		(400 MHz, DMSO-D6) d ppm 1.49–1.65(m, 2H) 1.75–1.86(m, 3H) 1.86–1.98(m, 3H) 2.53 (s, 1H) 2.88(s, 2H) 2.99(s, 2H) 5.84(s, 2H) 6.11 (d, J=6.57 Hz, 1H) 6.93(s, 1H) 7.28–7.38(m, J=8.08 Hz, 2H) 7.39–7.50(m, J=8.21, 8.21 Hz, 3H) 7.57(dd, J=8.72, 4.93 Hz, 1H) 7.81(s, 1H)	477	27

TABLE 3-continued

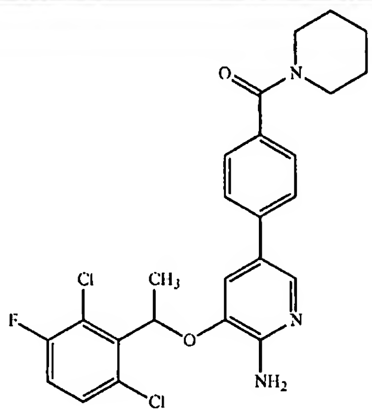
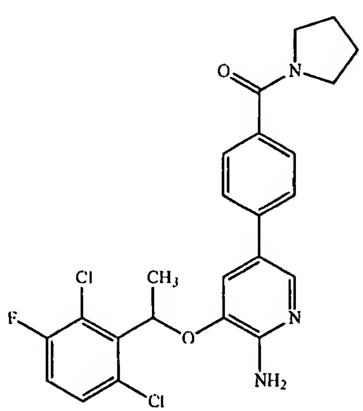
No.	Structure	Name	Ki (μM) or I (%)	¹H-NMR	MS m/z (M + H)	Procedure
I-546		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperidin-1-yl-methanone	0.057	(400 MHz, DMSO-D6) d ppm 1.43–1.56(m, 4H) 1.61(d, J=3.79 Hz, 4H) 1.81(d, J=6.57 Hz, 3H) 3.51(s, 2H) 5.94(s, 2H) 6.15(d, J=6.82 Hz, 1H) 7.00(d, J=1.77 Hz, 1H) 7.28–7.41(m, 2H) 7.40–7.50(m, 3H) 7.57(dd, J=9.09, 5.05 Hz, 1H) 7.87(d, J=2.02 Hz, 1H)	488	20
I-547		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-pyrrolidin-1-yl-methanone	0.067	(400 MHz, DMSO-D6) d ppm 1.73–1.93(m, 7H) 3.39–3.52(m, 4H) 5.96(s, 2H) 6.07–6.20(m, J=6.82 Hz, 1H) 6.99(d, J=1.77 Hz, 1H) 7.39–7.47(m, 3H) 7.52(d, 2H) 7.56(dd, J=9.09. 5.05 Hz, 1H) 7.82–7.92(m, J=1.77 Hz, 1H)	474	20

TABLE 3-continued

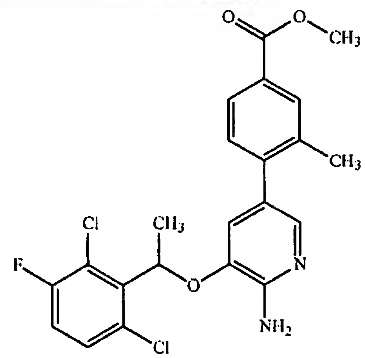
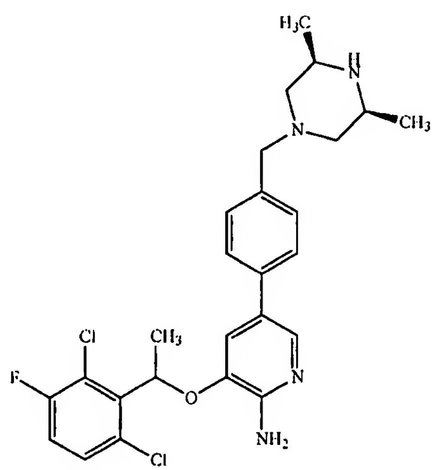
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-548		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-methyl-benzoic acid methyl ester	17%	(400 MHz, CHLOROFORM-D) d ppm 1.77–1.88 (m, 3H) 2.11(s, 3H) 3.91(s, 3H) 4.90(s, 2H) 6.02(d, J=6.82 Hz, 1H) 6.69(d, J=1.77 Hz, 1H) 7.00–7.09(m, 1H) 7.14(d, J=7.83 Hz, 1H) 7.26–7.31(m, 1H) 7.59(d, J=1.77 Hz, 1H) 7.83(dd, J=7.96, 1.39 Hz, 1H) 7.88(s, 1H)	450	19
I-549		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(dimethyl-piperazin-1-ylmethyl)-phenyl]-pyridin-2-ylamine	0.095	(400 MHz, DMSO-D6) d ppm 0.84–0.96(m, 6H) 1.44–1.61(m, 2H) 1.72–1.83(m, 3H) 2.58–2.70(m, 2H) 2.71–2.84(m, 4H) 5.76–5.92 (m, 2H) 6.02–6.18(m, 1H) 6.88–7.01(m, 1H) 7.25(d, 2H) 7.32(d, 2H) 7.38–7.49(m, 1H) 7.50–7.64(m, 2H) 7.76–7.88(m, 1H)	503	28

TABLE 3-continued

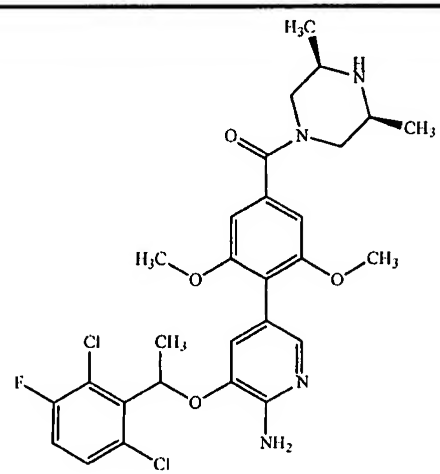
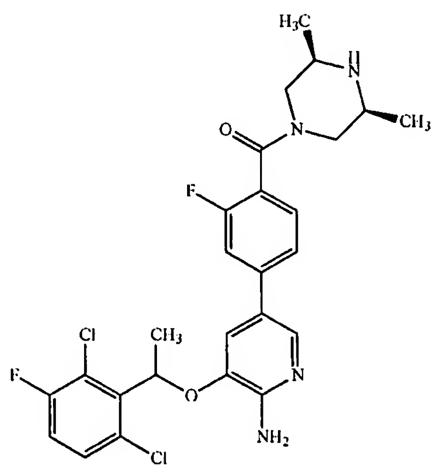
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-550		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3,5-dimethoxy-phenyl)-(dimethyl-piperazin-1-yl)-methanone	15%	(400 MHz, DMSO-D6) d ppm 0.77–0.91(m, 3H) 1.00(s, 3H) 1.75(d, J=6.82 Hz, 3H) 2.16–2.30 (m, J=12.63 Hz, 3H) 2.64–2.76(m, 3H) 3.54(s, 6H) 4.25–4.40(m, 1H) 5.69(s, 2H) 5.91(q, J=6.74 Hz, 1H) 6.54–6.67(m, 3H) 7.37–7.43 (m, 1H) 7.43–7.51(m, 1H) 7.51–7.60(m, 1H)	577	19/20
I-551		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone	0.091	(400 MHz, DMSO-D6) d ppm 0.80–0.96(m, 3H) 1.06(s, 3H) 1.80(d, J=6.57 Hz, 3H) 2.26–2.42 (m, J=1.52 Hz, 2H) 2.61–2.85(m, J=1.77 Hz, 3H) 4.35–4.47(m, J=6.32 Hz, 1H) 6.06(s, 2H) 6.16(q, J=6.57 Hz, 1H) 7.02(s, 1H) 7.27–7.40 (m, 3H) 7.40–7.49(m, J=8.72, 8.72 Hz, 2H) 7.51–7.62(m, J=8.84, 5.05 Hz, 1H) 7.93(s, 1H)	535	19/20

TABLE 3-continued

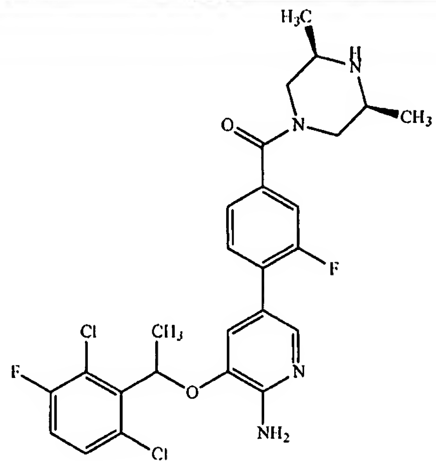
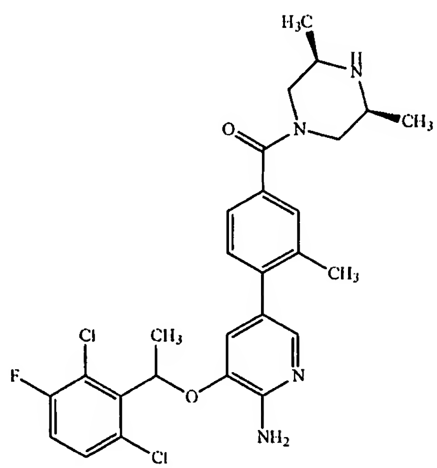
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-552		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone	0.2237	(400 MHz, DMSO-D6) d ppm 0.83–1.00(m, 3H) 1.02–1.17(m, 3H) 1.78(d, 3H) 2.70–2.98(m, 6H) 4.36–4.50(m, 1H) 6.01–6.10(m, 2H) 6.10–6.22(m, 1H) 6.96–7.04 (m, 1H) 7.06–7.15(m, 1H) 7.16–7.23(m. 1H) 7.30–7.39(m, 1H) 7.40–7.49(m, 1H) 7.50–7.59(m, 1H) 7.86–7.98(m, 1H)	535	19/20
I-553		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl)-3-methyl-phenyl)-(dimethyl-piperazin-1-yl)-methanone	0.2593	(400 MHz, DMSO-D6) d ppm 0.88(s, 3H) 1.01 (s, 3H) 1.77(d, J=6.57 Hz, 3H) 1.96(s, 3H) 2.31(s, 1H) 2.73(s, 3H) 3.50(s, 2H) 4.35(s, 1H) 5.89(s, 2H) 6.00(q, J=6.57 Hz, 1H) 6.60(s, 1H) 7.01–7.12(m, J=7.83 Hz, 1H) 7.12–7.28 (m, 2H) 7.37–7.63(m, 3H)	531	19/20

TABLE 3-continued

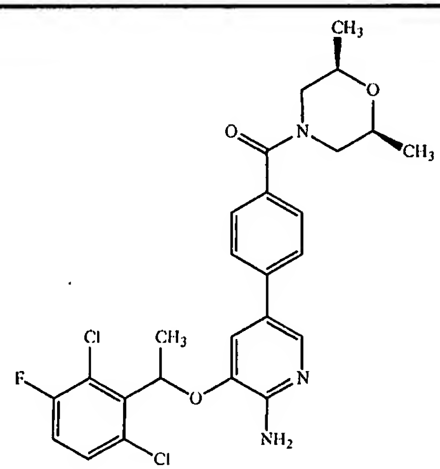
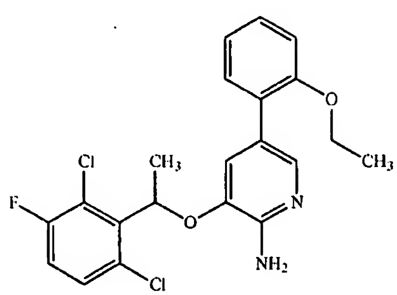
No.	Structure	Name	Ki (μM) or I (%)	¹H-NMR	MS m/z (M + H)	Procedure
I-554		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-methanone	0.1407	(400 MHz, DMSO-D6) d ppm 1.00–1.31(m, 4H) 1.87(d, J=6.82 Hz, 3H) 3.37–3.40(m, 6H) 3.55–3.65(m, 2H) 6.01–6.05(m, 2H) 6.21 (q, J=6.57 Hz, 1H) 7.07(d, J=1.77 Hz, 1H) 7.45–7.55(m, 5H) 7.63(dd, J=8.84, 5.05 Hz, 1H) 7.92–7.98(m, 1H)	518	19
I-555		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-ethoxy-phenyl)-pyridin-2-ylamine	22%	(400 MHz, DMSO-D6) d ppm 1.36(t, J=6.82 Hz, 3H) 1.95(d, J=6.57 Hz, 3H) 4.08–4.16(m, 2H) 5.91–5.95(m, 2H) 6.16(q, J=6.57 Hz, 1H) 7.08–7.13(m, 2H) 7.19(d, J=7.83 Hz, 1H) 7.27(dd, J=7.58, 1.77 Hz, 1H) 7.40(t, J=8.59 Hz, 1H) 7.62(t, J=8.59 Hz, 1H) 7.73(dd, J=9.09, 5.05 Hz, 1H) 7.84(d, J=1.77 Hz, 1H)	421	19

TABLE 3-continued

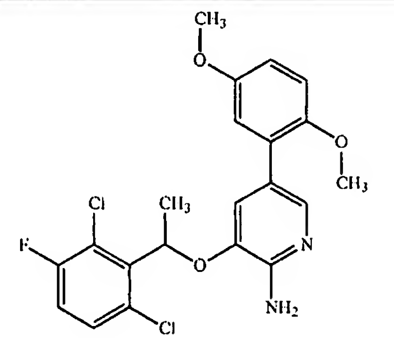
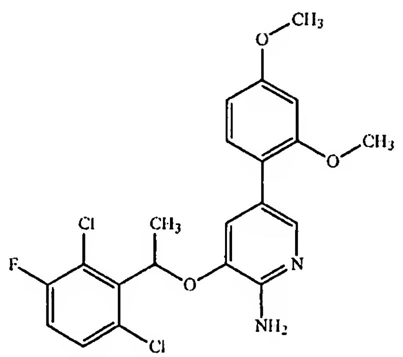
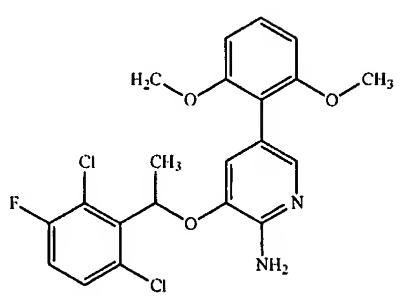
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-556		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethoxy-phenyl)-pyridin-2-ylamine	0.5746	(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.57 Hz, 3H) 3.57–3.58(m, 3H) 3.74–3.75(m, 3H) 5.82–5.86(m, 2H) 6.03(q, J=6.57 Hz, 1H) 6.72 (d, J=3.28 Hz, 1H) 6.84(dd, J=8.84, 3.03 Hz, 1H) 6.89(d, J=1.77 Hz, 1H) 6.98(d, J=9.09 Hz, 1H) 7.50(t, J=8.59 Hz, 1H) 7.61(dd, J=8.84, 4.80 Hz, 1H) 7.66(d, J=1.77 Hz, 1H)	4.37	19
I-557		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,4-dimethoxy-phenyl)-pyridin-2-ylamine	0.2172	(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.82 Hz, 3H) 3.64–3.67(m, 3H) 3.81–3.84(m, 3H) 5.74–5.78(m, 2H), 6.03(q, J32 6.57 Hz, 1H) 6.59 (dd, J=8.34, 2.27 Hz, 1H) 6.64(d, J=2.53 Hz, 1H) 6.88(d, J=1.77 Hz, 1H) 7.10(d, J=8.34 Hz, 1H) 7.53(t, J=8.59 Hz, 1H) 7.58(d, J=1.77 Hz, 1H) 7.63(dd, J=8.84, 5.05 Hz, 1H)	437	19
I-558		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethoxy-phenyl)-pyridin-2-ylamine	2%	(400 MHz, DMSO-D6) d ppm 1.81(d, J=6.82 Hz, 3H) 3.58–3.59(m, 6H) 5.68–5.69(m, 2H) 5.96(q, J=6.82 Hz, 1H) 6.63(d, J=1.77 Hz, 1H) 6.71(d, J=8.34 Hz, 2H) 7.26(t, J=8.34 Hz, 1H) 7.42(d, J=1.52 Hz, 1H) 7.52(t, J=8.59 Hz, 1H) 7.61(dd, J=8.84, 5.05 Hz, 1H)	437	19

TABLE 3-continued

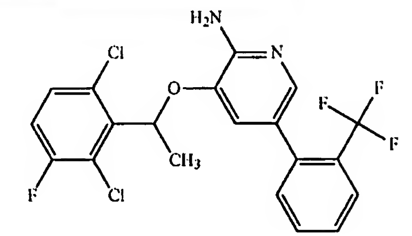
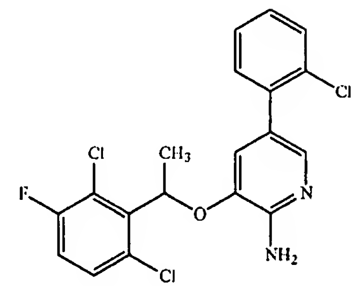
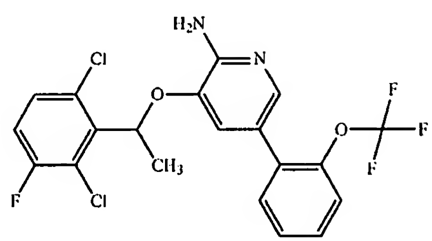
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-559		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine	4%	(400 MHz, DMSO-D6) d ppm 1.78(d, J=6.57 Hz, 3H) 5.91–5.99(m, 3H) 6.59–6.60(m, 1H) 7.26(d, J=7.58 Hz, 1H) 7.42–7.48(m, 2H) 7.50–7.58(m, 2H) 7.65(t, J=7.33 Hz, 1H) 7.75(d, J=7.83 Hz, 1H)	445	19
I-560		5-(2-Chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine	24%	(400 MHz, DMSO-D6) d ppm 1.79(d, J=6.82 Hz, 3H) 5.96–6.03(m, 3H) 6.75(d, J=1.77 Hz, 1H) 7.27–7.38(m, 3H) 7.42–7.49(m, 2H) 7.52–7.57(m, 2H)	411	19
I-561		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine	14%	(400 MHz, DMSO-D6) d ppm 1.74(d, J=6.82 Hz, 3H) 5.92–5.98(m, 3H) 6.74(d, J=1.77 Hz, 1H) 7.29–7.43(m, 5H) 7.50(dd, J=9.09, 5.05 Hz, 1H) 7.56(d, J=1.77 Hz, 1H)	461	19

TABLE 3-continued

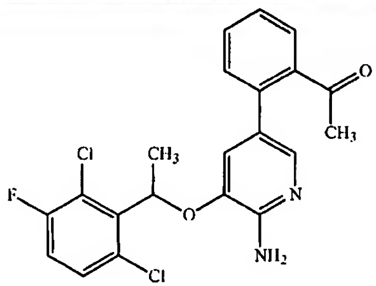
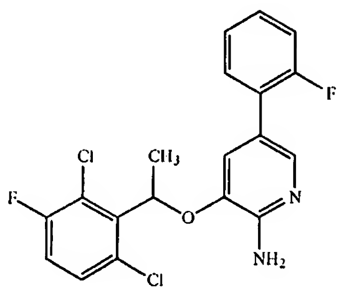
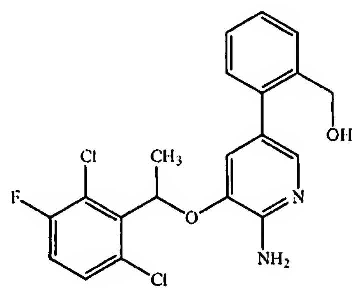
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-562		1-(2-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone	8%	(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.82 Hz, 3H) 1.92–1.93(m, 3H) 6.01–6.07(m, 3H) 6.59(d, J=2.02 Hz, 1H) 7.26(d, J=7.83 Hz, 1H) 7.45(t, J=7.33 Hz, 1H) 7.48–7.51(m, 1H) 7.52–7.58(m, 3H) 7.61(dd, J=8.84, 5.05 Hz, 1H)	419	19
I-563		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-fluoro-phenyl)-pyridin-2-ylamine	0.4322	(400 MHz, DMSO-D6) d ppm 1.71(d, J=6.57 Hz, 3H) 5.88–5.90(m, 2H) 5.96(q, J=6.82 Hz, 1H) 6.76–6.78(m, 1H) 7.10–7.16(m, 2H) 7.19–7.28(m, 2H) 7.36(t, J=8.59 Hz, 1H) 7.47(dd, J=8.84, 4.80 Hz, 1H) 7.60–7.63(m, 1H)	395	19
I-564		(2-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol	21%	(400 MHz, DMSO-D6) d ppm 1.79(d, J=6.57 Hz, 3H) 4.20(t, J=5.05 Hz, 2H) 5.03(t, J=5.56 Hz, 1H) 5.82–5.83(m, 2H) 6.02(q, J=6.57 Hz, 1H) 6.68(d, J=1.77 Hz, 1H) 7.01(dd, J=7.58, 1.52 Hz, 1H) 7.25(dt, J=7.58, 1.52 Hz, 1H) 7.31(dt, J=7.33, 1.26 Hz, 1H) 7.46(t, J=8.59 Hz, 1H) 7.49–7.53(m, 2H) 7.56(dd, J=8.84, 5.05 Hz, 1H)	407	19

TABLE 3-continued

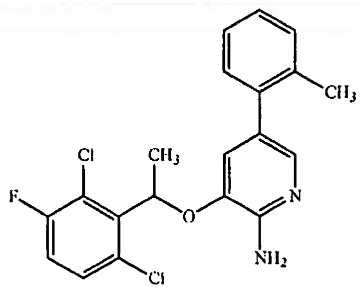
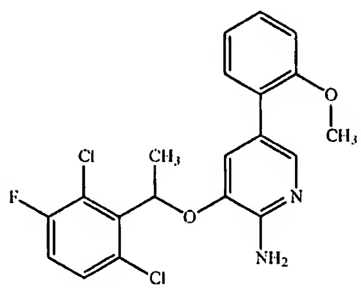
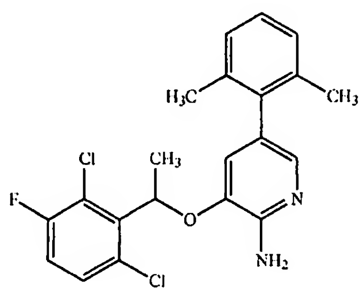
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-565		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-o-tolyl-pyridin-2-ylamine	25%	(400 MHz, DMSO-D6) d ppm 1.65(d, J=6.57 Hz, 3H) 1.80-1.80(m, 3H) 5.67-5.69(m, 2H) 5.86(q, J=6.57 Hz, 1H) 6.45(d, J=1.77 Hz, 1H) 6.86-6.90(m, 1H) 7.00-7.09(m, 3H) 7.29-7.35(m, 2H) 7.42(dd, J=8.84, 5.05 Hz, 1H)	391	19
I-566		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-methoxy-phenyl)-pyridin-2-ylamine	0.2779	(400 MHz, DMSO-D6) d ppm 1.84(d, J=6.57 Hz, 3H) 3.65-3.66(m, 3H) 5.83-5.84(m, 2H) 6.04(q, J=6.57 Hz, 1H) 6.93(d, J=1.77 Hz, 1H) 7.00(dt, J=7.33, 1.01 Hz, 1H) 7.08(d, J=7.83 Hz, 1H) 7.19(dd, J=7.58, 1.77 Hz, 1H) 7.28-7.34(m, 1H) 7.53(t, J=8.84 Hz, 1H) 7.61-7.66 (m, 2H)	407	19
I-567		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethyl-phenyl)-pyridin-2-ylamine	0%	(400 MHz, DMSO-D6) d ppm 1.57-1.58(m, 3H) 1.79(d, J=6.82 Hz, 3H) 1.97-1.98(m, 3H) 5.73-5.75(m, 2H) 5.98(q, J=6.57 Hz, 1H) 6.41 (d, J=1.77 Hz, 1H) 6.99-7.11(m, 3H) 7.25(d, J=1.77 Hz, 1H) 7.44(t, J=8.59 Hz, 1H) 7.54(dd, J=8.64, 5.05 Hz, 1H)	405	19

TABLE 3-continued

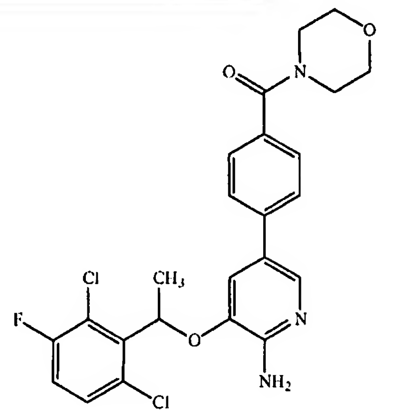
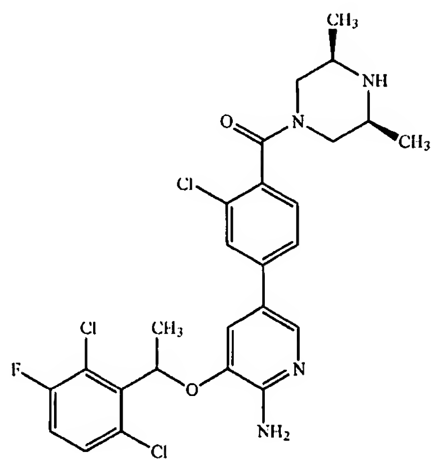
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-568		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-morpholin-4-yl-methanone	0.0525	Anal. Calcd for C24 H22 Cl2 F N3 O3: C, 58.79; H, 4.52; N, 8.57. Found: C, 58.39; H, 4.72; N, 8.24.	490	20
I-569		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-chloro-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone	0.0478	Anal. Calcd for C26 H26 Cl3 F N4 O2: C, 56.59; H, 4.75; N, 10.15. Found: C, 52.83; H, 5.16; N, 8.79. 1.1 eq of H2O; 1.3 eq AcOH	551	19/20

TABLE 3-continued

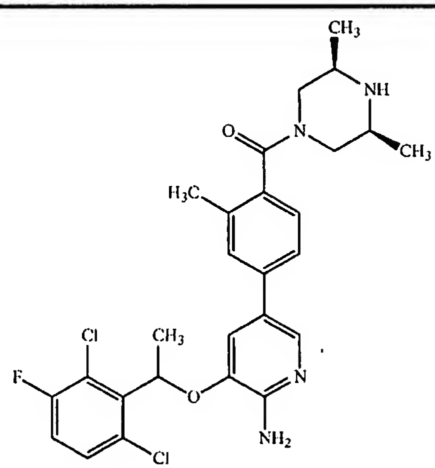
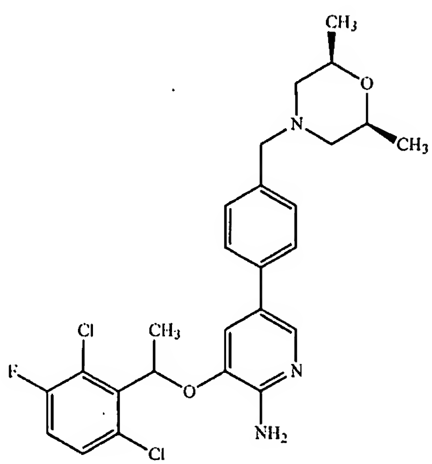
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-570		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-methyl-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone	0.225	Anal. Calcd for C27 H29 Cl2 F N4 O2: C, 61.02; H, 5.50; N, 10.54. Found: C, 55.99; H, 5.79; N, 9.01. 1.2 eq of H2O; 1.5 eq of AcOH	531	19/20
I-571		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-((2R,6S)-2,6-dimethyl-morpholin-4-ylmethyl)-phenyl]-pyridin-2-ylamine	0.2204	(400 MHz, CHLOROFORM-D) d ppm 1.09(d, J=6.32 Hz, 6H) 1.80(d, J=6.82 Hz, 3H) 1.88–1.98(m, 2H) 2.78–2.90(m, 2H) 3.59–3.70(m, 2H) 3.86–3.95 (m, 2H) 5.12–5.16(m, 2H) 6.06(q, J=6.57 Hz, 1H) 6.94–7.04(m, 2H) 7.25 (dd, J=8.84, 4.80 Hz, 1H) 7.28–7.34(m, 2H) 7.36–7.44(m, 2H) 7.77(d, J=1.52 Hz, 1H)	504	28

TABLE 3-continued

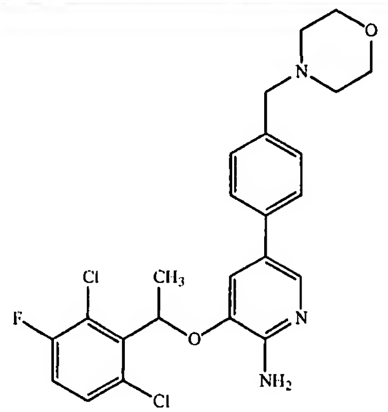
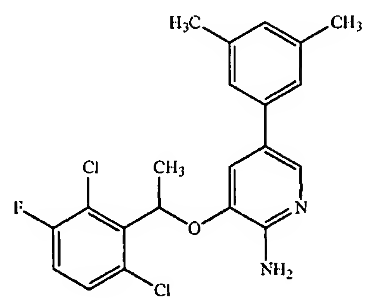
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-572		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-morpholin-4-ylmethyl-phenyl)-pyridin-2-ylamine	0.0554	(400 MHz, CHLOROFORM-D) d ppm 1.80(d, J=6.57 Hz, 3H) 2.51–2.58(m, 4H) 3.58–3.60 (m, 2H) 3.75(t, J=4.55 Hz, 4H) 5.27–5.31(m, 2H) 6.06(q, J=6.57 Hz, 1H) 6.95(d, J=1.52 Hz, 1H) 7.00(t, J=8.08 Hz, 1H) 7.22–7.29(m, 3H) 7.33–7.37(m, 2H) 7.74(d, J=1.77 Hz, 1H)	476	28
I-573		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dimethyl-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.64(d, J=6.57 Hz, 3H) 2.08–2.10(m, 6H) 5.65–5.68(m, 2H) 5.93(q, J=6.57 Hz, 1H) 6.69–6.71(m, 2H) 6.75–6.78(m, 2H) 7.28(t, J=8.59 Hz, 1H) 7.40(dd, J=9.09, 4.80 Hz, 1H) 7.62(d, J=1.77 Hz, 1H)	405	19

TABLE 3-continued

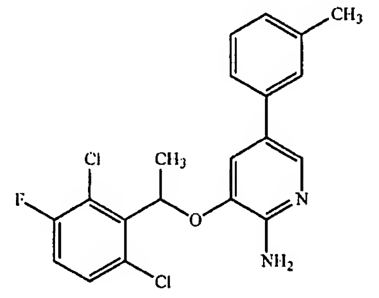
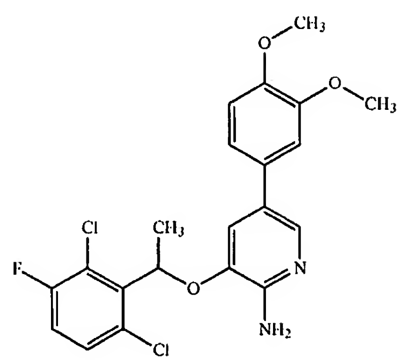
No.	Structure	Name	Ki (μM) or I (%)	¹H-NMR	MS m/z (M + H)	Procedure
I-574		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-m-tolyl-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.78(d, J=6.57 Hz, 3H) 2.27-2.28(m, 3H) 5.80-5.84(m, 2H) 6.08(q, J=6.57 Hz, 1H) 6.88(d, J=1.77 Hz, 1H) 7.02(d, J=7.33 Hz, 1H) 7.09-7.15(m, 2H) 7.21 (t, J=7.58 Hz, 1H) 7.41(t, J=8.59 Hz, 1H) 7.54 (dd, J=9.09, 5.05 Hz, 1H) 7.77(d, J=1.77 Hz, 1H)	391	19
I-575		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dimethoxy-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.60(d, J=6.57 Hz, 3H) 3.55(d, J=14.91 Hz, 6H) 5.57-5.60(m, 2H) 5.90(q, J=6.57 Hz, 1H) 6.63(d, J=2.02 Hz, 1H) 6.65(d, J=1.77 Hz, 1H) 6.68-6.76(m, 2H) 7.23(t, J=8.59 Hz, 1H) 7.36(dd, J=4.80, 4.04 Hz, 1H) 7.58(d, J=1.77 Hz, 1H)	437	19

TABLE 3-continued

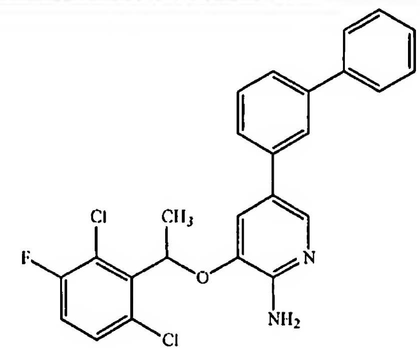
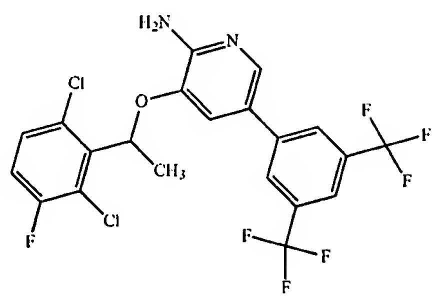
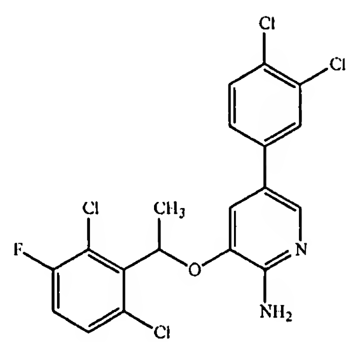
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-576		5-Biphenyl-3-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 5.92–5.95(m, 2H) 6.16(q, J=6.57 Hz, 1H) 7.01(d, J=1.52 Hz, 1H) 7.38–7.59(m, 9H) 7.69 (d, J=7.33 Hz, 2H) 7.93(d, J=1.52 Hz, 1H)	453	19
I-577		5-(3,5-Bis-trifluoromethyl-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.84(d, J=6.57 Hz, 3H) 6.16–6.24(m, 3H) 7.03(d, J=1.77 Hz, 1H) 7.45(t, J=8.59 Hz, 1H) 7.54(dd, J=9.09, 5.05 Hz, 1H) 7.92–7.95(m, 1H) 8.00–8.02(m, 2H) 8.08(d, J=2.02 Hz, 1H)	513	19
I-578		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.87(d, J=6.57 Hz, 3H) 6.09–6.12(m, 2H) 6.22(q, J=8.57 Hz, 1H) 7.04(d, J=1.77 Hz, 1H) 7.46–7.53(m, 2H) 7.62 (dd, J=9.09, 5.05 Hz, 1H) 7.66–7.70(m, 2H) 7.96(d, J=2.02 Hz, 1H)	446	19

TABLE 3-continued

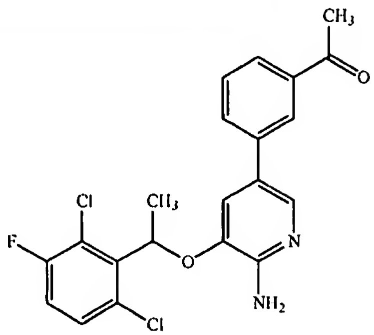
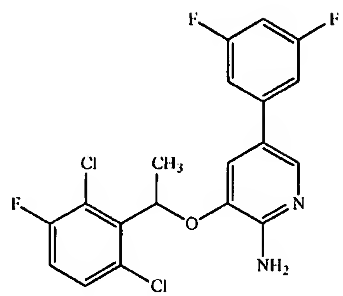
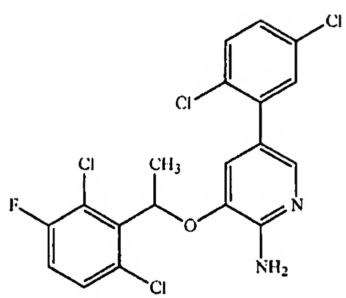
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-579		1-(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone		(400 MHz, DMSO-D6) d ppm 1.76(d, J=6.57 Hz, 3H) 2.54–2.55(m, 3H) 5.90–5.94(m, 2H) 6.10(q, J=6.57 Hz, 1H) 6.93(d, J=1.77 Hz, 1H) 7.39(t, J=8.59 Hz, 1H) 7.46(t, J=7.83 Hz, 1H) 7.51(dd, J=9.09, 5.05 Hz, 1H) 7.63(d, J=8.34 Hz, 1H) 7.76(d, J=7.83 Hz, 1H) 7.81–7.83(m, 1H) 7.85(d, J=2.02 Hz, 1H)	419	19
I-580		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-difluoro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.57 Hz, 3H) 6.06–6.10(m, 2H) 6.18(q, J=6.57 Hz, 1H) 7.01(d, J=1.77 Hz, 1H) 7.06–7.19(m, 3H) 7.45 (t, J=8.84 Hz, 1H) 7.58(dd, J=9.09, 5.05 Hz, 1H) 7.95(d, J=2.02 Hz, 1H)	413	19
I-581		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dichloro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.90(d, J=6.82 Hz, 3H) 6.10(q, J=6.57 Hz, 1H) 6.17–6.19(m, 2H) 6.84(d, J=1.77 Hz, 1H) 7.44–7.51(m, 2H) 7.56 (t, J=8.59 Hz, 1H) 7.59–7.70(m, 3H)	446	19

TABLE 3-continued

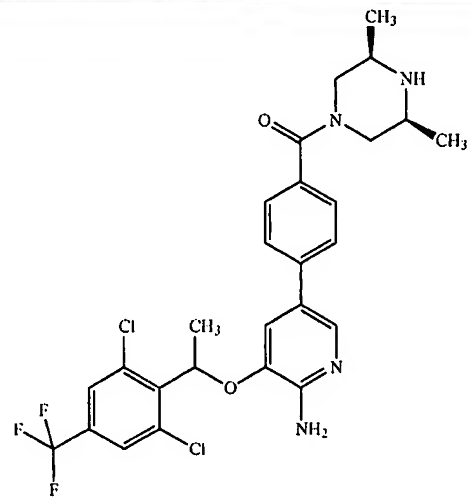
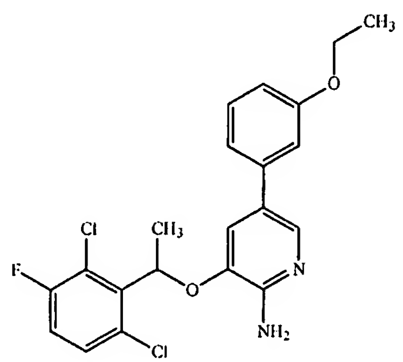
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-582		(4-{6-Amino-5-[1-(2,6-dichloro-4-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone		Passed CHN 1.0 eq AcOH	567	18/20
I-583		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-ethoxy-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.35(t, J=6.82 Hz, 3H) 1.82(d, J=6.57 Hz, 3H) 3.99–4.09(m, 2H) 5.88–5.91(m, 2H) 6.13(q, J=6.57 Hz, 1H) 6.80 (dd, J=8.08, 2.27 Hz, 1H) 6.84(t, J=2.02 Hz, 1H) 6.92(d, J=1.77 Hz, 1H) 6.96(d, J=7.58 Hz, 1H) 7.26(t, J=7.83 Hz, 1H) 7.46(t, J=8.59 Hz, 1H) 7.57(dd, J=8.84, 5.05 Hz, 1H) 7.83(d, J=1.77 Hz, 1H)	421	19

TABLE 3-continued

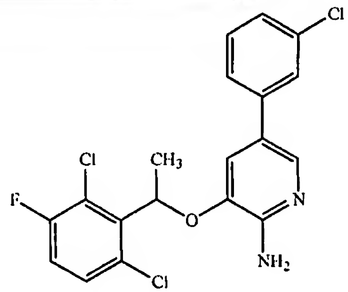
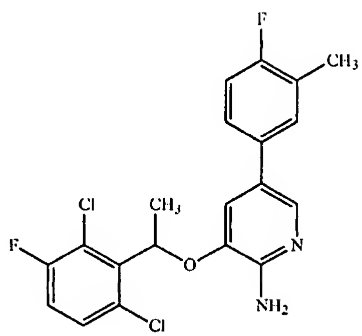
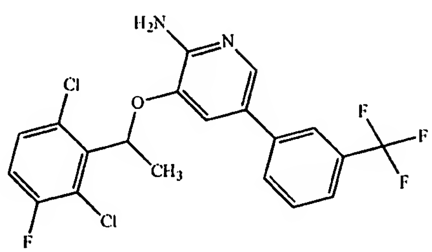
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-584		5-(3-Chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.87(d, J=6.57 Hz, 3H) 6.03-6.06(m, 2H) 6.18-6.24(m, 1H) 7.02(d, J=2.02 Hz, 1H) 7.35(td, J=6.82, 1.77 Hz, 1H) 7.41-7.53(m, 4H) 7.62(dd, J=8.84, 5.05 Hz, 1H) 7.93(d, J=2.02 Hz, 1H)	411	19
I-585		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-3-methyl-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.58(d, J=6.57 Hz, 3H) 2.01-2.02(m, 3H) 5.62-5.64(m, 2H) 5.89(q, J=6.82 Hz, 1H) 6.68(d, J=1.77 Hz, 1H) 6.90(t, J=8.84 Hz, 1H) 6.96-7.04(m, 2H) 7.22 (t, J=8.59 Hz, 1H) 7.34(dd, J=9.09, 5.05 Hz, 1H) 7.56(d, J=1.77 Hz, 1H)	409	19
I-586		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethyl-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.84(d, J=6.57 Hz, 3H) 6.05-6.07(m, 2H) 6.14-6.21(m, 1H) 6.99(d, J=1.77 Hz, 1H) 7.46(t, J=8.59 Hz, 1H) 7.56(dd, J=8.84, 5.05 Hz, 1H) 7.59-7.65(m, 3H) 7.76-7.80(m, 1H) 7.95(d, J=1.77 Hz, 1H)	445	19

TABLE 3-continued

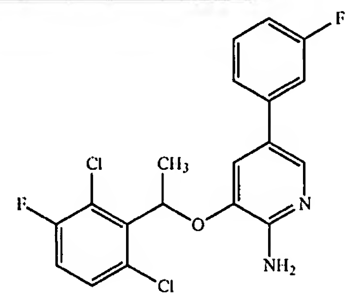
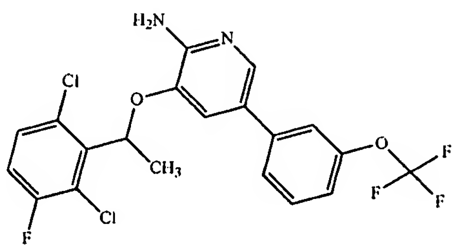
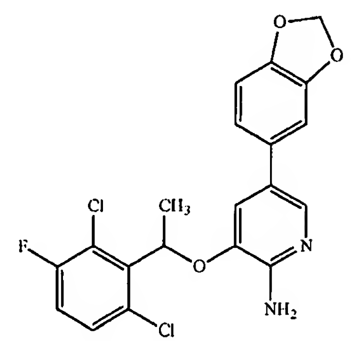
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-587		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-fluoro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.57 Hz, 3H) 5.98–6.00(m, 2H) 6.13–6.20(m, 1H) 6.99(d, J=1.77 Hz, 1H) 7.05–7.11(m, 1H) 7.21–7.27(m, 2H) 7.39–7.49(m, 2H) 7.59(dd, J=9.09, 5.05 Hz, 1H) 7.90(d, J=2.02 Hz, 1H)	395	19
I-588		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethoxy-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.60(d, J=6.57 Hz, 3H) 5.80–5.84(m, 2H) 5.90–5.98(m, 1H) 6.73(d, J=2.02 Hz, 1H) 7.00–7.07(m, 2H) 7.20–7.30(m, 3H) 7.34(dd, J=8.84, 4.80 Hz, 1H) 7.68(d, J=1.77 Hz, 1H)	461	19
I-589		5-Benzo[1,3]dioxol-5-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.57 Hz, 3H) 5.81–5.83(m, 2H) 6.03–6.04(m, 2H) 6.10–6.17(m, 1H) 6.83–6.96(m, 4H) 7.46(t, J=8.84 Hz, 1H) 7.58(dd, J=9.09, 5.05 Hz, 1H) 7.76(d, J=2.02 Hz, 1H)	421	19

TABLE 3-continued

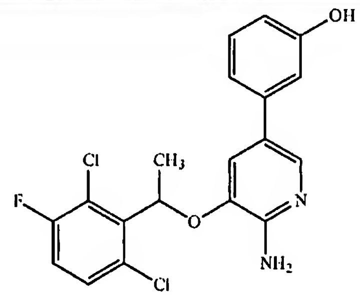
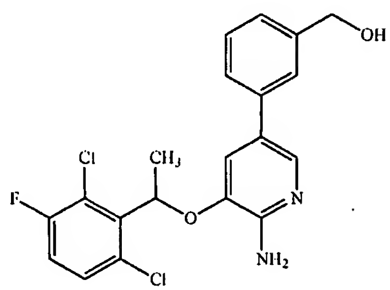
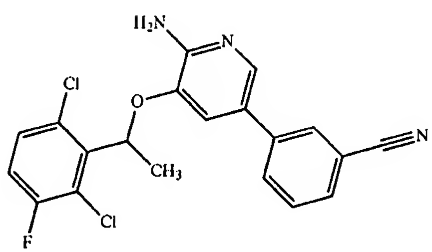
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-590		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenol		(400 MHz, DMSO-D6) d ppm 1.95(d, J=6.82 Hz, 3H) 5.98-6.00(m, 2H) 6.22-6.28(m, 1H) 6.78-6.81(m, 1H) 6.89-6.93(m, 2H) 7.04(d, J=1.77 Hz, 1H) 7.29(t, J=8.08 Hz, 1H) 7.58(t, J=9.09, 8.59 Hz, 1H) 7.71(dd, J=8.84, 4.80 Hz, 1H) 7.89(d, J=1.77 Hz, 1H) 9.55-9.57(m, 1H)	393	19
I-591		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 4.52(d, J=5.31 Hz, 2H) 5.16-5.22(m, 1H) 5.88-5.90(m, 2H) 6.11-6.17(m, 1H) 6.96(d, J=1.52 Hz, 1H) 7.20-7.28(m, 2H) 7.31-7.36 (m, 2H) 7.46(t, J=8.84 Hz, 1H) 7.58(dd, J=9.09, 5.05 Hz, 1H) 7.83(d, J=1.77 Hz, 1H)	407	19
I-592		3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile		(400 MHz, DMSO-D6) d ppm 1.88(d, J=8.57 Hz, 3H) 6.10-6.12(m, 2H) 6.24(q, J=6.57 Hz, 1H) 7.12(d, J=1.77 Hz, 1H) 7.51(t, J=8.59 Hz, 1H) 7.60-7.68(m, 2H) 7.77(d, J=7.83 Hz, 1H) 7.81 (d, J=8.08 Hz, 1H) 7.94-7.96(m, 1H) 8.00(d, J=1.77 Hz, 1H)	402	19

TABLE 3-continued

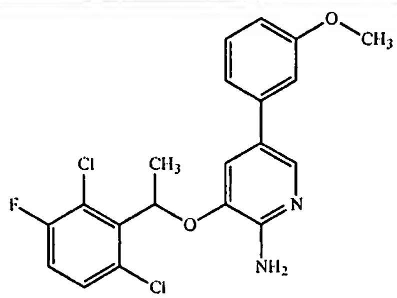
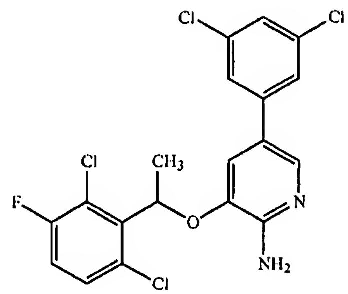
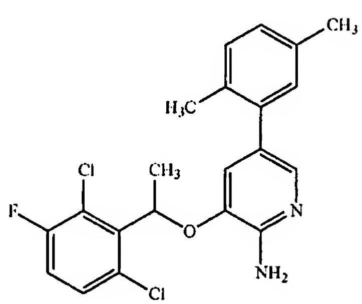
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-593		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-methoxy-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 3.79–3.80(m, 3H) 5.91–5.92(m, 2H) 6.11–6.18(m, 1H) 6.81–6.84(m, 1H) 6.86–6.89(m, 1H) 6.93(d, J=1.52 Hz, 1H) 6.97–7.01 (m, 1H) 7.29(t, J=8.34, 7.83 Hz, 1H) 7.46(t, J=8.84 Hz, 1H) 7.59(dd, J=9.09, 5.05 Hz, 1H) 7.85(d, J=1.77 Hz, 1H)	407	19
I-594		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dichloro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 6.10–6.12(m, 2H) 6.16–6.22(m, 1H) 7.00(d, J=1.77 Hz, 1H) 7.44–7.49(m, 4H) 7.58 (dd, J=9.09, 5.31 Hz, 1H) 7.95(d, J=2.02 Hz, 1H)	446	19
I-595		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethyl-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.80(d, J=6.82 Hz, 3H) 1.90–1.93(m, 3H) 2.24–2.27(m, 3H) 5.81–5.83(m, 2H) 6.00(q, J=6.82, 6.32 Hz, 1H) 6.57(d, J=1.77 Hz, 1H) 6.79–6.82(m, 1H) 6.98–7.03(m, 1H) 7.10(d, J=7.83 Hz, 1H) 7.45–7.52(m, 2H) 7.58(dd, J=8.84, 5.05 Hz, 1H)	405	19

TABLE 3-continued

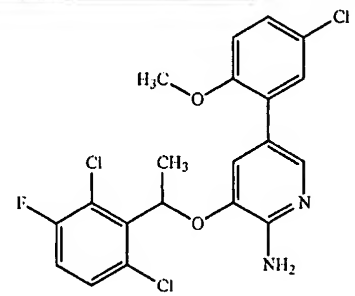
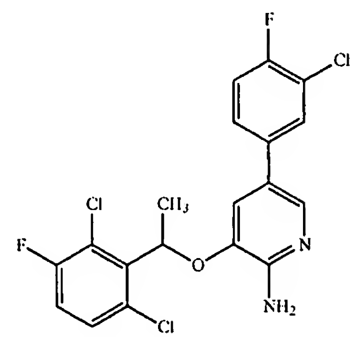
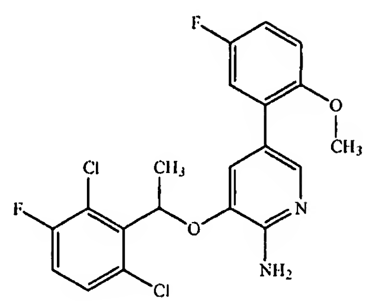
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-596		5-(5-Chloro-2-methoxy-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.79(d, J=6.57 Hz, 3H) 3.61–3.63(m, 3H) 5.89–5.91(m, 2H) 5.97–6.03(m, 1H) 6.86(d, J=1.77 Hz, 1H) 7.06 (d, J=8.84 Hz, 1H) 7.15(d, J=2.78 Hz, 1H) 7.29 (dd, J=8.84, 2.53 Hz, 1H) 7.49(t, J=8.59 Hz, 1H) 7.59(dd, J=9.09, 5.31 Hz, 1H) 7.63(d, J=1.77 Hz, 1H)	441	19
I-597		5-(3-Chloro-4-fluoro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 5.98–6.00(m, 2H) 6.14–6.20(m, 1H) 6.98(d, J=1.77 Hz, 1H) 7.42–7.45(m, 2H) 7.47 (d, J=8.59 Hz, 1H) 7.55–7.60(m, 2H) 7.87 (d, J=2.02 Hz, 1H)	429	19
I-598		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(5-fluoro-2-methoxy-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.79(d, J=6.57 Hz, 3H) 3.59–3.60(m, 3H) 5.88–5.91(m, 2H) 6.00 (q, J=6.82 Hz, 1H) 6.90(d, J=1.77 Hz, 1H) 6.99–7.10(m, 3H) 7.48(t, J=8.84 Hz, 1H) 7.59 (dd, J=9.09, 5.31 Hz, 1H) 7.64(d, J=2.02 Hz, 1H)	425	19

TABLE 3-continued

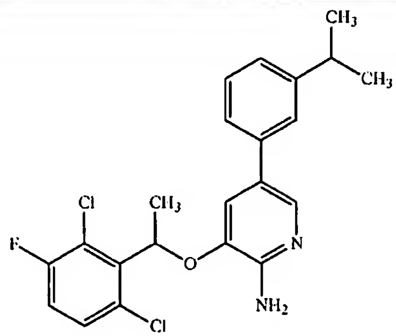
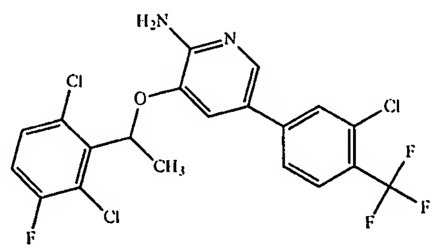
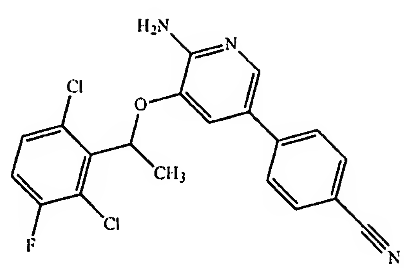
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-599		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-isopropyl-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.20–1.25(m, 6H) 1.83(d, J=6.57 Hz, 3H) 2.86–2.94(m, 1H) 5.88–5.91(m, 2H) 6.13(q, J=6.32 Hz, 1H) 6.89 (d, J=1.77 Hz, 1H) 7.11–7.15(m, 2H) 7.23–7.31(m, 2H) 7.47(t, J=8.59 Hz, 1H) 7.58(dd, J=8.84, 4.80 Hz, 1H) 7.83(d, J=2.02 Hz, 1H)	419	19
I-600		5-(3-Chloro-4-trifluoro-methyl-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 6.11–6.13(m, 2H) 6.17(q, J=6.57 Hz, 1H) 6.99(d, J=1.77 Hz, 1H) 7.46(t, J=8.84 Hz, 1H) 7.56(dd, J=9.09, 5.05 Hz, 1H) 7.68(d, J=1.77 Hz, 1H) 7.72(d, J=8.59 Hz, 1H) 7.80(dd, J=8.34, 1.77 Hz, 1H) 7.95(d, J=2.02 Hz, 1H)	478.90	19
I-601		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile		(400 MHz, DMSO-D6) d ppm 1.83(d, J=6.57 Hz, 3H) 6.13–6.22(m, 3H) 7.06(d, J=1.77 Hz, 1H) 7.45(t, J=8.59 Hz, 1H) 7.57(dd, J=9.09, 5.05 Hz, 1H) 7.63(d, J=8.59 Hz, 2H) 7.84(d, J=8.59 Hz, 2H) 7.97(d, J=1.77 Hz, 1H)	402	19

TABLE 3-continued

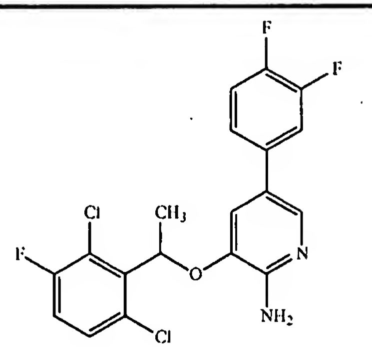
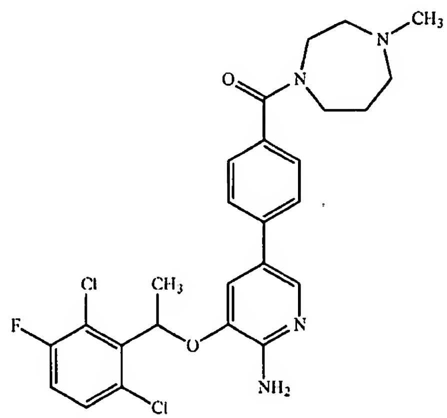
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-602		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.82 Hz, 3H) 5.96-6.00(m, 2H) 6.17(q, J=6.57 Hz, 1H) 6.99(d, J=1.77 Hz, 1H) 7.22–7.27(m, 1H) 7.41–7.52(m, 3H) 7.58(dd, J=9.09, 5.05 Hz, 1H) 7.87(d, J=2.02 Hz, 1H)	413	19
I-603		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-[1,4]-diazepan-1-yl)-methanone	0.0095	(400 MHz, DMSO-D6) d ppm 1.73(m, 1H) 1.80 (d, J=6.82 Hz, 3H) 1.84(m, 1H) 2.26 (d, J=21.98 Hz, 2H) 2.53(m, 2H) 2.63(m, 2H) 3.40 (m, 2H) 3.60(m, 2H) 5.95(s, 2H) 6.14(d, J=6.57 Hz, 1H) 6.99(s, 1H) 7.36(d, J=7.58 Hz, 2H) 7.44(m, 3H) 7.57(dd, J=8.97, 4.93 Hz, 1H) 7.86(d, J=1.77 Hz, 1H)	517	20

TABLE 3-continued

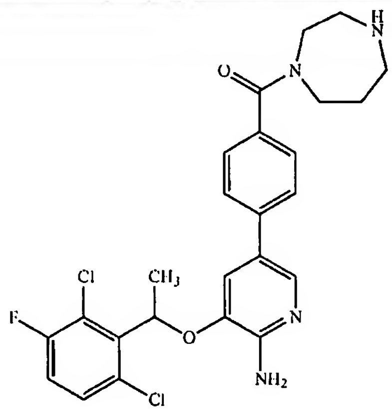
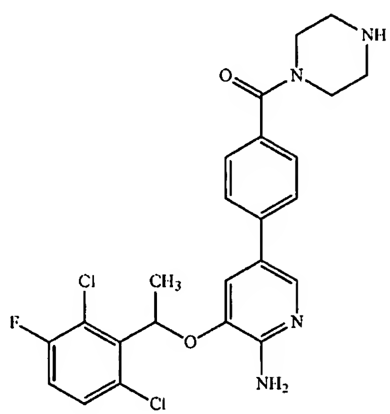
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-604		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[1,4]diazepan-1-yl-methanone	0.031	(400 MHz, DMSO-D6) d ppm 1.81(t, J=6.19 Hz, 3H) 1.90(m, 2H) 2.96(m, 2H) 3.10(d, J=36.88 Hz, 2H) 3.45(m, 2H) 3.7(m, 2H) 5.96(s, 2H) 6.14(q, J=6.82 Hz, 1H) 6.99(d, J=1.52 Hz, 1H) 7.44(m, 5H) 7.56(dd, J=8.97, 4.93 Hz, 1H) 7.87(d, J=1.77 Hz, 1H)	503	20/21
I-605		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperazin-1-yl-methanone	0.0475	(400 MHz, DMSO-D6) d ppm 1.80(d, J=6.57 Hz, 3H) 2.72(m, 4H) 3.36(m, 2H) 3.52(m, 2H) 5.96 (s, 2H) 6.14(q, J=6.74 Hz, 1H) 6.99(d, J=1.77 Hz, 1H) 7.37(m, 2H) 7.44(m, 3H) 7.57(dd, J=8.97, 4.93 Hz, 1H) 7.87(d, J=1.77 Hz, 1H)	489	20/21

TABLE 3-continued

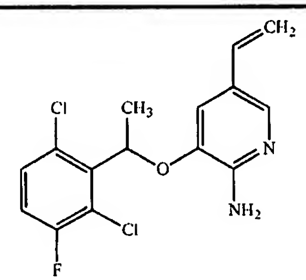
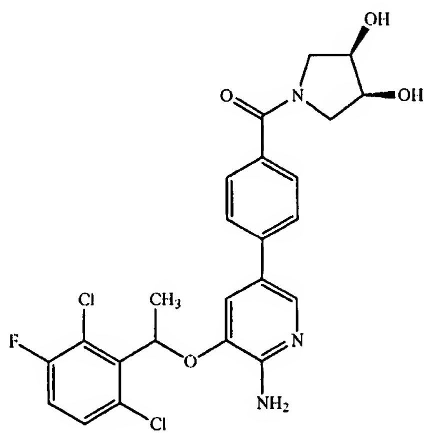
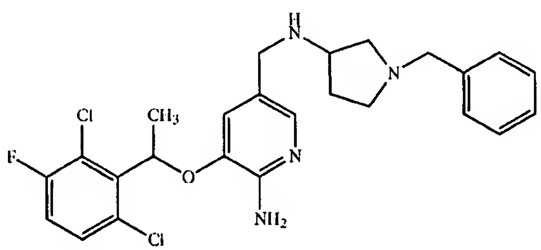
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-606		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine	0.655	(400 MHz, CHLOROFORM-D) d ppm 1.83(d, J=6.57 Hz, 3H) 4.84(s, 2H) 5.03(d, J=11.12 Hz, 1H) 5.38(d, J=17.43 Hz, 1H) 6.06(q, J=6.82 Hz, 1H) 6.49(dd, J=17.68, 10.86 Hz, 1H) 6.90(d, J=1.77 Hz, 1H) 7.04(dd, J=8.84, 7.83 Hz, 1H) 7.29(dd, J=8.84, 4.80 Hz, 1H) 7.55(d, J=1.77 Hz, 1H)	327	19
I-607		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-methanone	0.058	(400 MHz, DMSO-D6) d ppm 1.81(d, J=6.82 Hz, 3H) 3.28(m, 2H) 3.54(m, 2H) 3.97(d, J=4.04 Hz, 2H) 4.08(d, J=4.29 Hz, 2H) 5.10(br, 2H) 5.98(d, 2H) 7.00(d, J=1.77 Hz, 1H) 7.45(m, 3H) 7.48(m, 2H) 7.57(dd, J=8.97, 4.93 Hz, 1H) 7.88(d, J=1.77 Hz, 1H)	506	20/21
I-608		5-[(1-Benzyl-pyrrolidin-3-ylamino)-methyl]-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine	0%	(400 MHz, DMSO-D6) d ppm 1.34(m, 1H) 1.74 (d, J=5.94 Hz, 3H) 1.78(m, 1H) 2.08(m, 1H) 2.40(m, 2H) 2.54(m, 1H) 2.89(m, 1H) 3.33(s, 2H) 3.49(s, 2H) 5.52(s, 2H) 5.94(q, J=6.57 Hz, 1H) 6.68(s, 1H) 7.27(m, 5H) 7.36(m, 1H) 7.39(m, 1H) 7.48(m, 1H)	489	23

TABLE 3-continued

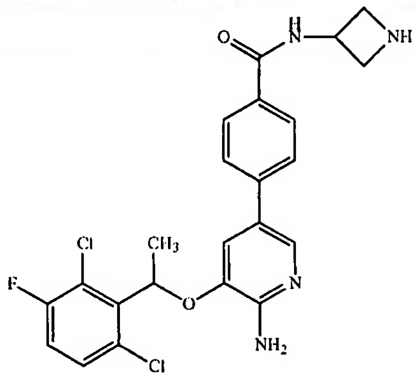
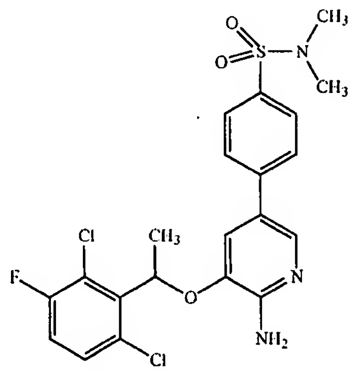
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-609		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-azetidin-3-yl-benzamide	0.045	(400 MHz, DMSO-D6) d ppm 1.80(d, J=6.57 Hz, 3H) 2.87(m, 1H) 3.43(m, 1H) 3.81(m, 2H) 4.74(m, 1H) 6.00(s, 2H) 6.13(q, J=6.48 Hz, 1H) 6.96(dd, J=6.57, 1.77 Hz, 1H) 7.45(m, 3H) 7.54 (dd, J=8.97, 4.93 Hz, 1H) 7.87(m, 3H)	475	20/21
I-610		4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N,N-dimethyl-benzenesulfonamide	0.069	(400 MHz, CHLOROFORM-D) d ppm 1.87(d, J=6.82 Hz, 3H) 2.72(s, 6H) 4.99(s, 2H) 6.12 (q, J=6.57 Hz, 1H) 6.99(d, J=1.77 Hz, 1H) 7.07(m, 1H) 7.32(dd, J=8.84, 4.80 Hz, 1H) 7.50(m, 2H) 7.76(d, J=8.59 Hz, 2H) 7.91(d, J=1.77 Hz, 1H)	484	29

TABLE 3-continued

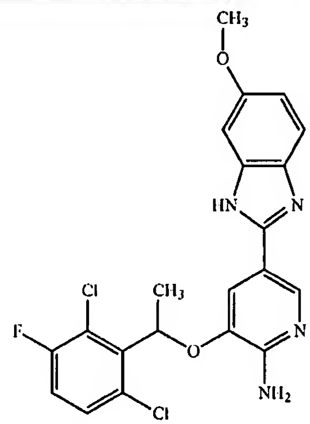
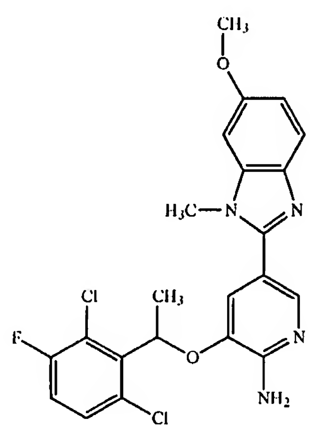
No.	Structure	Name	Ki (µM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-611		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1H-benzoimidazol-2-yl)-pyridin-2-ylamine		(400 MHz, MeOD) d ppm 1.72(d, J=6.57 Hz, 3H) 3.69(s, 3H) 4.78(s, 2H) 6.13(q, J=6.57 Hz, 1H) 6.71(dd, J=8.84, 2.27 Hz, 1H) 6.88(d, J=2.02 Hz, 1H) 7.04(m, 1H) 7.26(m, 2H) 7.40 (d, J=1.77 Hz, 1H) 8.03(d, J=2.02 Hz, 1H)	447	24
I-612		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1-methyl-1H-benzoimidazol-2-yl)-pyridin-2-ylamine		(400 MHz, MeOD) d ppm 1.78(d, J=6.57 Hz, 3H) 3.51(s, 3H) 3.75(s, 3H) 6.10(q, J=6.32 Hz, 1H) 6.90(m, 1H) 6.92(m, 1H) 7.13(m, 1H) 7.35(m, 2H) 7.80(d, J=7.33 Hz, 1H)	461	24

TABLE 3-continued

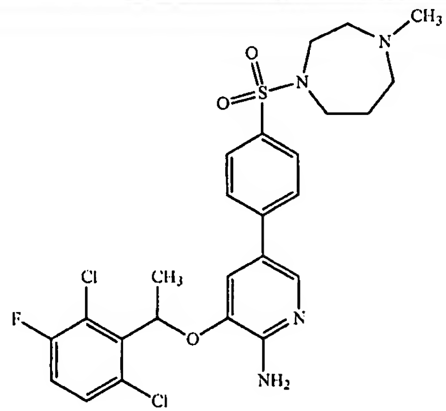
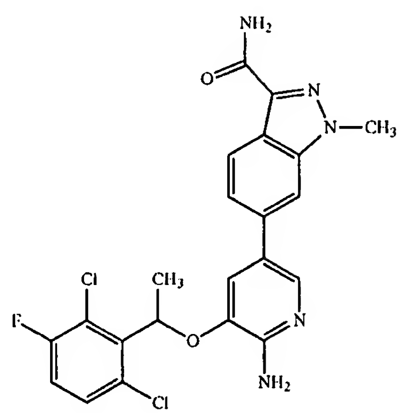
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-613		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(4-methyl-[1,4]-diazepane-1-sulfonyl)-phenyl]-pyridin-2-ylamine		(400 MHz, McOD) d ppm 1.83(m, 2H) 1.87(d, J=6.57 Hz, 3H) 2.66(m, 4H) 3.35(m, 2H) 3.40 (m, 2H) 6.20(q, J=6.65 Hz, 1H) 7.02(d, J=1.77 Hz, 1H) 7.20(t, J=8.59 Hz, 1H) 7.43(dd, J=8.97, 4.93 Hz, 1H) 7.54(d, J=8.34 Hz, 2H) 7.77(d, J=8.59 Hz, 2H) 7.81(d, J=1.26 Hz, 1H)	553	29
I-614		6-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1-methyl-1H-indazole-3-carboxylic acid amide		(400 MHz, DMSO-D6) d ppm 1.82(d, J=6.57 Hz, 3H) 3.92(s, 3H) 5.96(s, 2H) 6.17(q, J=6.48 Hz, 1H) 7.03(d, J=1.77 Hz, 1H) 7.35(dd, J=8.59, 1.26 Hz, 1H) 7.44(t, J=8.72 Hz, 1H) 7.56(m, 2H) 7.91(d, J=2.02 Hz, 1H) 8.03(d, J=8.59 Hz, 1H)	475	26

TABLE 3-continued

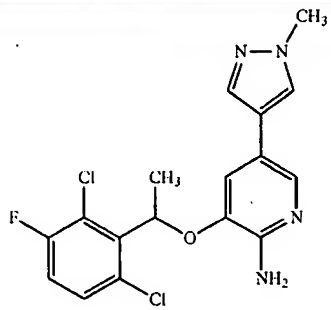
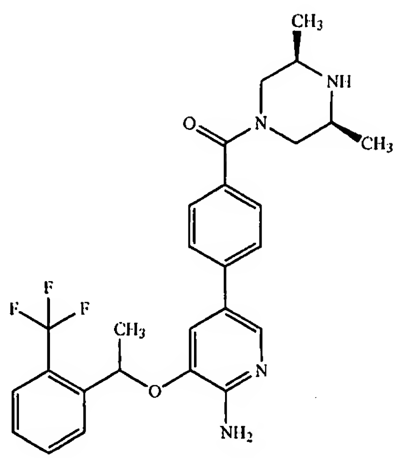
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-615		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-ylamine		(400 MHz, CHLOROFORM-D) d ppm 1.84(d, J=6.82 Hz, 3H) 3.89(s, 3H) 4.76(s, 2H) 6.05 (q, J=6.57 Hz, 1H) 6.84(d, J=1.77 Hz, 1H) 7.03 (m, 1H) 7.28(dd, J=8.97, 4.93 Hz, 1H) 7.40(s, 1H) 7.53(s, 1H) 7.74(d, J=1.77 Hz, 1H)	381	19
I-616		(4-{6-Amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone	3%	(400 MHz, DMSO-D6) d ppm 9.29(d, J=9.60 Hz, 1H) 8.63(d, J=10.86 Hz, 1H) 7.84–7.94 (m, 2H) 7.72(t, J=7.96 Hz, 3H) 7.47–7.57(m, 6H) 7.35(s, 1H) 5.97–6.05(m, 1H) 3.37(s, 2H) 1.69 (d, J=6.06 Hz, 3H) 1.15(s, 5H) 1.06(s, 1H)	500	33

TABLE 3-continued

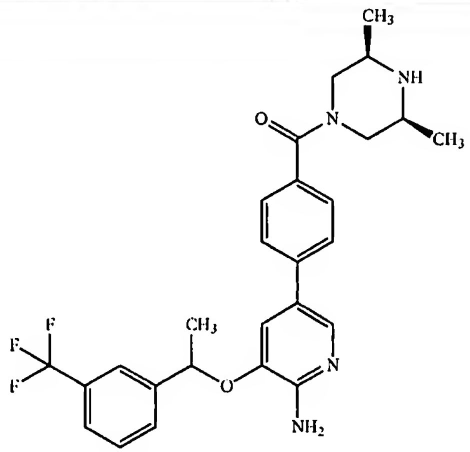
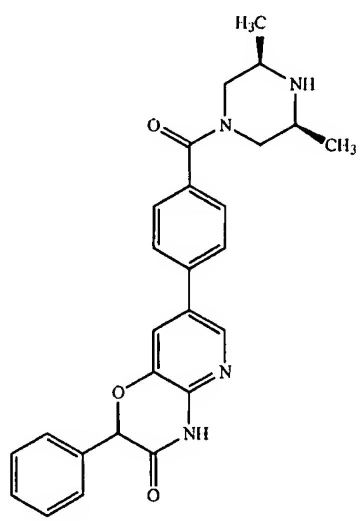
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-617		(4-{6-Amino-5-[1-(3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone	2%	(400 MHz, DMSO-D6) d ppm 9.26(s, 2H) 8.64 (s, 2H) 7.93(s, 2H) 7.84(d, J=1.52 Hz, 2H) 7.81(d, J=7.58 Hz, 2H) 7.66(s, 2H) 7.60(d, J=8.34 Hz, 5H) 7.53–7.59(m, 2H) 7.46(d, J=8.34 Hz, 4H) 6.01(q, J=6.32 Hz, 2H) 3.32(s, 4H) 3.03(s, 1H) 2.75(s, 1H) 1.61(d, J=6.32 Hz, 5H) 1.13(s, 7H)	500	32
I-618		7-[4-(3,5-Dimethyl-piperazine-1-carbonyl)-phenyl]-2-phenyl-4H-pyrido[3,2-b][1,4]oxazin-3-one	0%	(400 MHz, DMSO-D6) d ppm 8.53(s, 2H) 8.33 (d, J=2.02 Hz, 2H) 7.84(d, J=2.02 Hz, 2H) 7.80 (d, J=8.34 Hz, 5H) 7.36–7.42(m, 12H) 5.93(s, 2H) 4.55(s, 1H) 3.73(s, 3H) 3.40(s, 6H) 1.19(s, 10H)	444	32

TABLE 3-continued

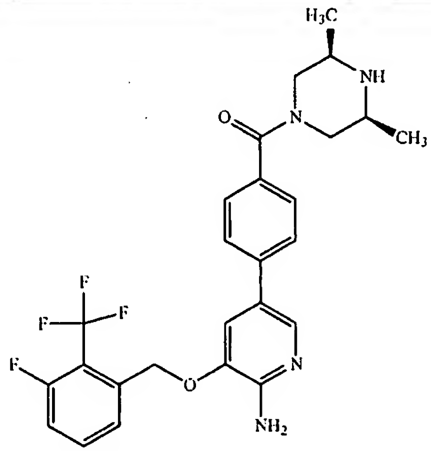
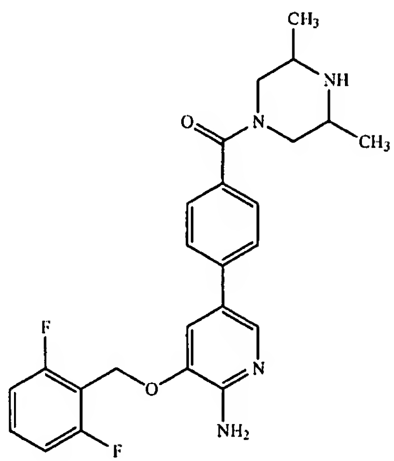
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-619		{4-[6-Amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	16%	(400 MHz, DMSO-D6) d ppm 7.97(d, J=1.77 Hz, 1H) 7.79(s, 1H) 7.66–7.74(m, 3H) 7.48 (d, J=1.77 Hz, 2H) 7.41(d, J=8.34 Hz, 2H) 7.24(s, 1H) 5.91(s, 1H) 5.40(s, 2H) 3.61(s, 1H) 2.61–2.70(m, 3H) 2.33(s, 1H) 2.17(s, 1H) 1.95–2.06(m, 1H) 1.47(s, 1H) 1.23(s, 7H) 1.00(s, 3H) 0.80–0.92(m, 6H)	504	32
I-620		{4-[6-Amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	5%	(400 MHz, DMSO-D6) d ppm 8.02(s, 1H) 7.96 (s, 1H) 7.85(d, J=8.34 Hz, 2H) 7.51–7.62(m, 3H) 7.23(t, J=8.08 Hz, 2H) 5.43(s, 2H) 4.09(s, 1H) 3.37(s, 1H) 1.40(s, 9H) 1.14(d, J=2.27 Hz, 3H) 1.08(d, J=16.42 Hz, 3H)	454	34

TABLE 3-continued

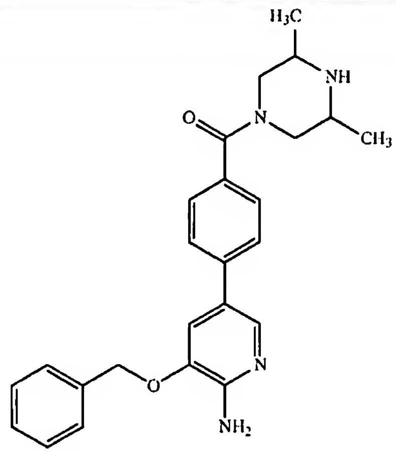
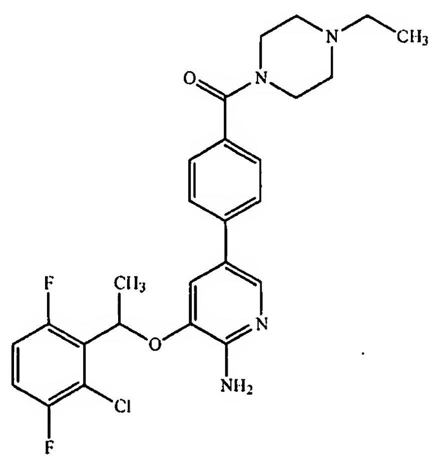
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-621		[4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(3,5-dimethyl-piperazin-1-yl)-methanone	6%	(400 MHz, DMSO-D6) d ppm 9.35(s, 1H) 8.70 (s, 1H) 7.96(s, 2H) 7.78(d, J=8.59 Hz, 4H) 7.55(d, J=8.08 Hz, 5H) 7.42(t, J=7.20 Hz, 2H) 7.35(t, J=7.33 Hz, 1H) 5.40(s, 2H) 3.39(s, 2H) 3.16(s, 1H) 1.20(s, 4H)	418	34
I-622		(4-{6-Amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone	0.375	(400 MHz, DMSO-D6) d ppm 7.95(d, J=1.77 Hz, 1H) 7.57(d, J=8.34 Hz, 2H) 7.52(s, 1H) 7.45 (d, J=8.08 Hz, 3H) 7.25(d, J=1.77 Hz, 1H) 6.11 (s, 1H) 5.95(s, 2H) 3.62(s, 1H) 3.49(s, 1H) 2.44(s, 2H) 2.41(d, J=7.07 Hz, 4H) 1.85(d, J=6.32 Hz, 3H) 1.06(t, J=7.20 Hz, 3H)	502	4

TABLE 3-continued

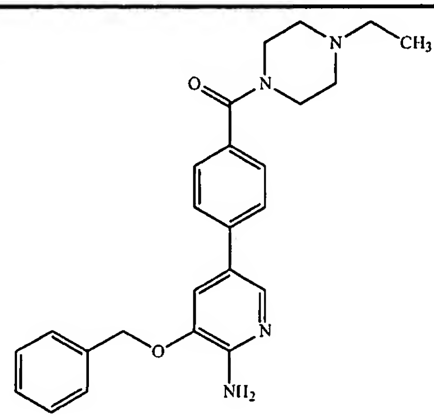
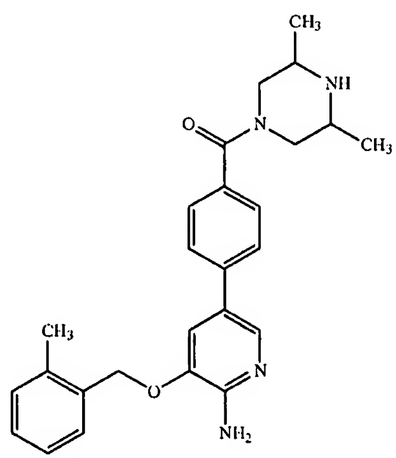
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-623		[4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-ethyl-piperazin-1-yl)-methanone	7%	(400 MHz, DMSO-D6) d ppm 7.91(d, J=2.02 Hz, 1H) 7.65(d, J=8.34 Hz, 2H) 7.53(d, J=7.33 Hz, 2H) 7.44(d, J=1.77 Hz, 1H) 7.37–7.42(m, 3H) 7.32(t, J=7.33 Hz, 1H) 5.94(s, 2H) 5.25(s, 2H) 3.60(s, 1H) 3.38(s, 1H) 2.30 2.41(m, 5H) 0.99(t, J=7.20 Hz, 3H)	418	34
I-624		{4-[6-Amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	0%	(400 MHz, DMSO-D6) d ppm 9.40(s, 1H) 8.77 (s, 1H) 7.98(d, J=1.52 Hz, 1H) 7.77–7.88(m, 4H) 7.57(d, J=8.34 Hz, 2H) 7.53(d, J=7.33 Hz, 1H) 7.21–7.31(m, 3H) 5.37(s, 2H) 3.39(s, 2H) 2.37(s, 3H) 1.20(s, 4H)	432	34

TABLE 3-continued

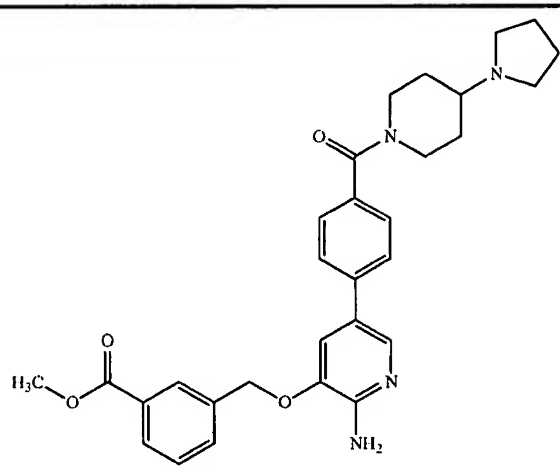
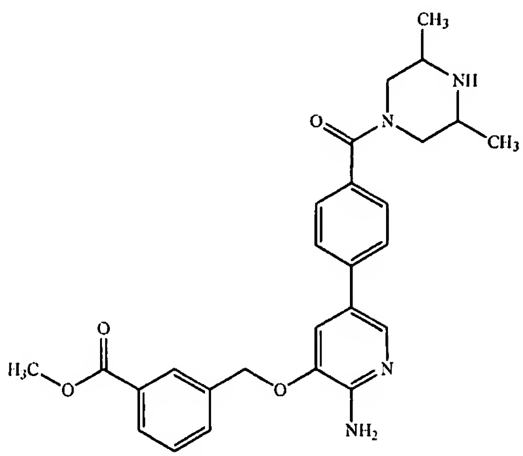
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-625		3-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester	6%	(400 MHz, DMSO-D6) d ppm 9.78(s, 1H) 8.12 (s, 1H) 7.92–7.98(m, 2H) 7.88(d, J=7.58 Hz, 1H) 7.74–7.83(m, 3H) 7.59(t, J=7.71 Hz, 2H) 7.48(d, J=8.34 Hz, 2H) 5.47(s, 2H) 3.86(s, 3H) 3.50(s, 2H) 3.41(s, 1H) 3.10(s, 2H) 2.00 (s, 3H) 1.85(s, 2H) 1.53(s, 2H)	516	6
I-626		3-{2-Amino-5-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester	0%	(400 MHz, DMSO-D6) d ppm 9.31(s, 2H) 8.67 (s, 2H) 8.12(s, 2H) 7.92–7.99(m, 4H) 7.88(d, J=7.83 Hz, 2H) 7.75–7.84(m, 6H) 7.53–7.63 (m, 6H) 5.48(s, 4H) 3.81–3.91(m, 6H) 3.39 (s, 4H) 3.13(s, 1H) 1.20(s, 7H)	476	34

TABLE 3-continued

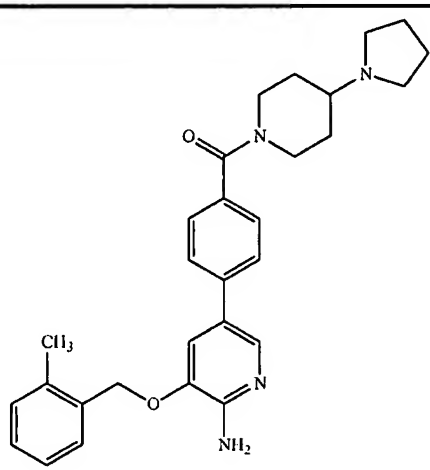
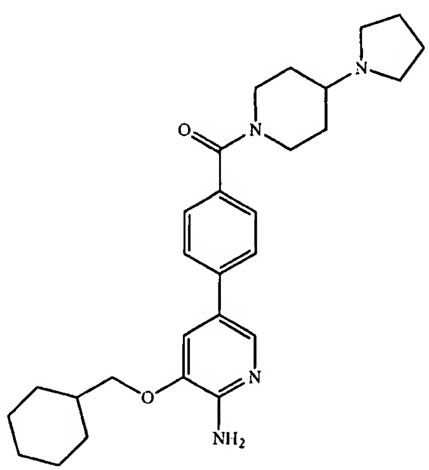
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-627		{4-[6-Amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	6%	(400 MHz, DMSO-D6) d ppm 9.91(s, 1H) 7.95 (d, J=1.52 Hz, 1H) 7.85(s, 1H) 7.80(d, J=8.34 Hz, 2H) 7.53(d, J=7.07 Hz, 1H) 7.49(d, J=8.34 Hz, 2H) 7.21–7.31(m, 3H) 5.36(s, 2H) 4.56 (s, 1H) 3.68(s, 1H) 3.51(s, 2H) 3.41(s, 1H) 3.10(s, 3H) 2.82(s, 1H) 2.37(s, 3H) 1.99(s, 3H) 1.79–1.90(m, 2H) 1.56(s, 2H)	472	6
I-628		[4-(6-Amino-5-cyclo-hexylmethoxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	7%	(400 MHz, DMSO-D6) d ppm 7.90(d, J=1.52 Hz, 1H) 7.79(d, J=8.34 Hz, 3H) 7.66(s, 1H) 7.44–7.55(m, 2H) 4.03(d, J=6.06 Hz, 2H) 3.83(s, 1H) 3.67(s, 1H) 3.51(s, 2H) 3.39(s, 1H) 3.09 (s, 2H) 2.82(s, 1H) 2.14(s, 2H) 1.99(s, 3H) 1.79–1.91(m, 5H) 1.64–1.76(m, 3H) 1.54(s, 2H) 1.20–1.30(m, 2H) 1.07(d, J=11.62 Hz, 2H)	464	6

TABLE 3-continued

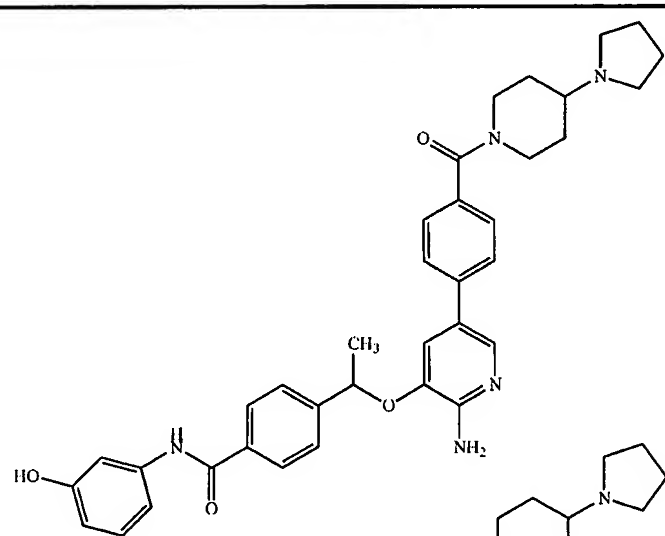
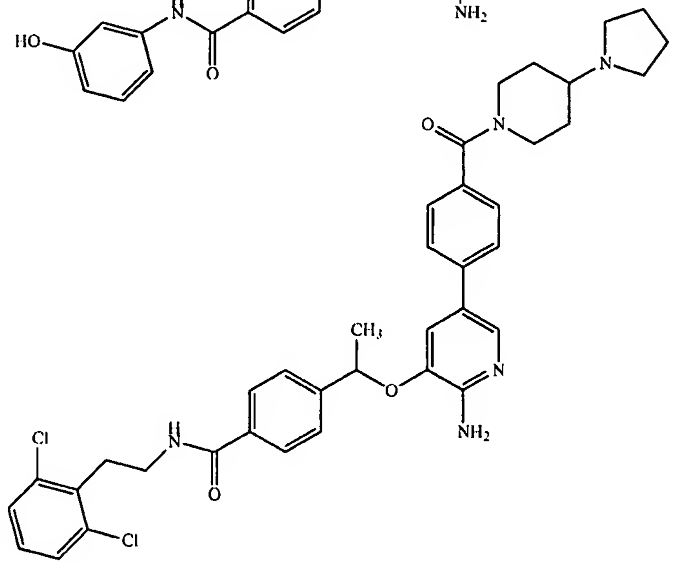
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-629		4-(1-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(3-hydroxy-phenyl)-ethyl]-benzamide	7%	(400 MHz, DMSO-D6) d ppm 9.76(s, 1H) 8.51 (t, J=5.56 Hz, 1H) 7.86(d, J=1.52 Hz, 2H) 7.79 (d, J=8.34 Hz, 2H) 7.63(dd, J=14.40, 8.34 Hz, 5H) 7.45(d, J=8.34 Hz, 2H) 7.04(t, J=7.96 Hz, 1H) 6.55–6.65(m, 3H) 6.00(d, J=6.32 Hz, 1H) 3.49(s, 2H) 3.34–3.45(m, 3H) 3.09(s, 3H) 2.75(s, 1H) 2.65–2.74(m, 2H) 2.13(s, 1H) 1.99(s, 3H) 1.78–1.89(m, 2H) 1.65(d, J=6.32 Hz, 3H) 1.52(s, 2H)	635	6
I-630		4-(1-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(2,6-dichloro-phenyl)-ethyl]-benzamide	3%	(400 MHz, DMSO-D6) d ppm 9.80(s, 1H) 8.62 (t, J=5.81 Hz, 1H) 7.85(d, J=1.26 Hz, 1H) 7.78 (d, J=8.34 Hz, 3H) 7.62(dd, J=12.63, 8.34 Hz, 5H) 7.39–7.49(m, 4H) 7.21–7.30(m, 1H) 5.98 (d, J=6.32 Hz, 1H) 3.65(s, 1H) 3.40–3.51(m, J=6.63, 6.63, 6.63, 6.63 Hz, 4H) 3.03–3.15(m, 5H) 2.82(s, 1H) 2.13(s, 1H) 1.98(s, 3H) 1.78–1.89(m, 2H) 1.65(d, J=6.06 Hz, 3H) 1.53(s, 2H)	688	6

TABLE 3-continued

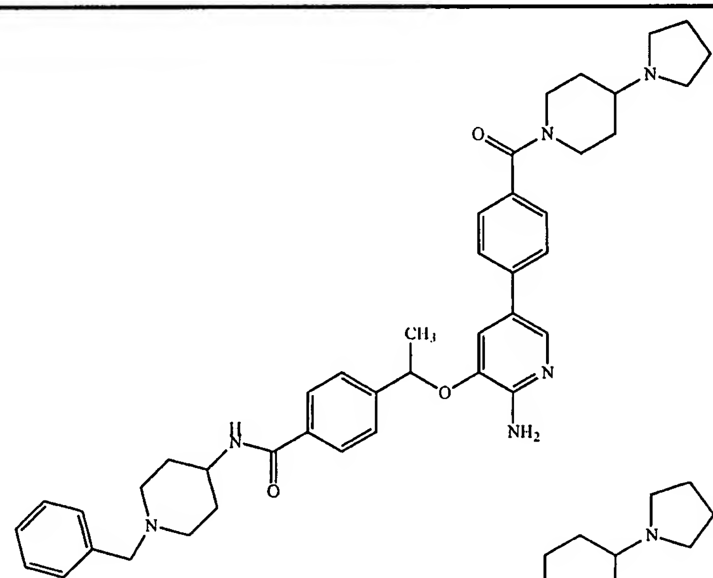
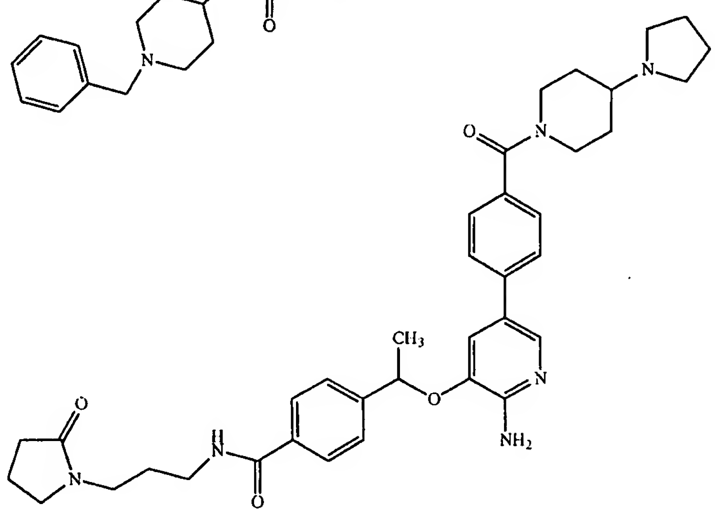
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-631		4-(1-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-(1-benzyl-piperidin-4-yl)-benzamide	3%	(400 MHz, DMSO-D6) d ppm 7.75–7.82(m, 2H) 7.56–7.67(m, 4H) 7.39–7.49(m, 6H) 4.27 (d, J=4.80 Hz, 2H) 3.92(s, 1H) 3.49(s, 2H) 3.37 (s, 2H) 3.07(s, 3H) 2.12(s, 1H) 1.92–2.04(m, 4H) 1.79–1.91(m, 2H) 1.71(d, J=11.87 Hz, 1H) 1.59–1.68(m, 3H) 1.51(s, 2H)	688	4
I-632		4-(1-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-benzamide	0%	(400 MHz, DMSO-D6) d ppm 8.39(s, 1H) 7.77–7.85(m, 3H) 7.61(t, J=8.08 Hz, 6H) 7.43 (d, J=8.34 Hz, 2H) 5.96(s, 1H) 3.69(s, 2H) 3.49 (s, 3H) 3.39(s, 2H) 3.30(t, J=6.95 Hz, 3H) 3.14–3.22(m, 4H) 3.09(s, 3H) 2.18(t, J=8.08 Hz, 2H) 2.00(s, 3H) 1.86(ddd, J=15.28, 7.58, 7.45 Hz, 4H) 1.65(t, J=6.06 Hz, 5H) 1.52(s, 2H)	640	6

TABLE 3-continued

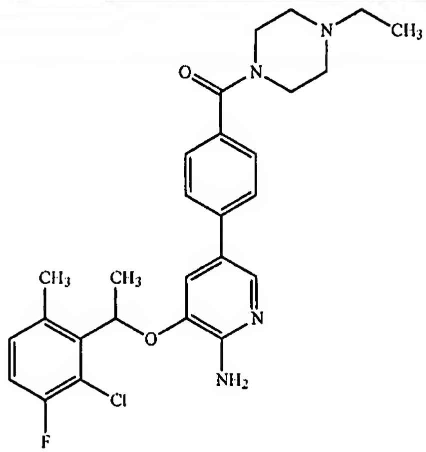
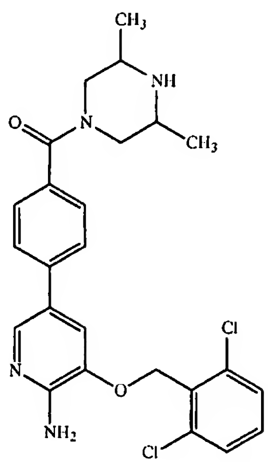
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-633		(4-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperizin-1-yl)-methanone	0.0472	(400 MHz, DMSO-D6) d ppm 9.85(s, 1H) 7.91 (d, J=1.77 Hz, 1H) 7.58(dd, J=8.97, 4.93 Hz, 1H) 7.50–7.55(m, 4H) 7.44–7.50(m, 1H) 7.13 (d, J=1.52 Hz, 1H) 6.27(q, J=6.57 Hz, 1H) 3.48 (s, 2H) 3.15(q, J=7.07 Hz, 3H) 3.06(s, 2H) 1.84(d, J=6.57 Hz, 3H) 1.22(t, J=7.33 Hz, 3H)	518	6
I-634		{4-[6-Amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	10%	(400 MHz, DMSO-D6) d ppm 9.29(s, 2H) 8.66(s, 2H) 7.91–8.00(m, 5H) 7.85(d, J=6.82 Hz, 5H) 7.54–7.61(m, 10H) 7.48–7.53(m, 3H) 5.48(s, 5H) 4.61(s, 1H) 1.21(d, J=4.55 Hz, 9H) 1.15(s, 5H)	486	34

TABLE 3-continued

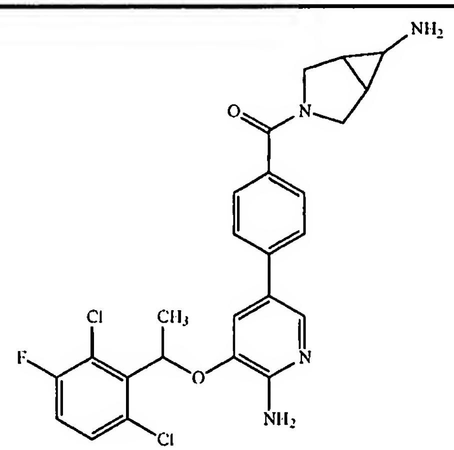
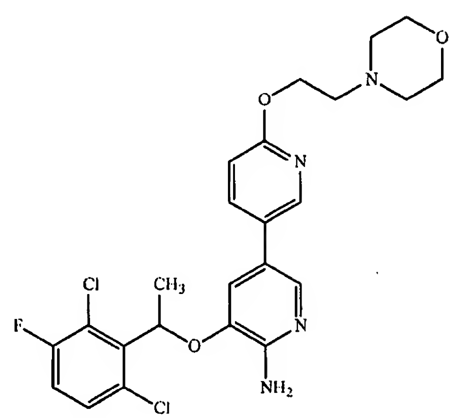
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-635		(6-Amino-3-aza-bicyclo[3.1.0]hex-3-yl)-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanone	0.0554	(400 MHz, DMSO-D6) d ppm 8.14(d, J=3.54 Hz, 3H) 7.87(s, 1H) 7.58(dd, J=8.97, 4.93 Hz, 1H) 7.44–7.53(m, 5H) 7.12(s, 1H) 6.25(s, 1H) 3.95(d, J=11.87 Hz, 1H) 3.69(s, 2H) 1.96(d, J=13.39 Hz, 2H) 1.84(d, J=6.57 Hz, 3H)	502	35
I-636		5-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-morpholin-4-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine	0.109	(400 MHz, DMSO-D6) d ppm 8.20(d, J=2.27 Hz, 1H) 7.83(d, J=1.77 Hz, 1H) 7.79(dd, J=8.59, 2.53 Hz, 1H) 7.61(dd, J=8.97, 4.93 Hz, 1H) 7.49(t, J=8.84 Hz, 1H) 6.98(d, J=1.77 Hz, 1H) 6.88(d, J=8.59 Hz, 1H) 6.18(q, J=6.82 Hz, 1H) 5.92(s, 2H) 4.41(t, J=5.81 Hz, 2H) 3.61(m, 4H) 2.72(t, J=5.81 Hz, 2H) 2.47–2.52(m, 4H) 1.85(d, J=6.57 Hz, 3H)	507	36

TABLE 3-continued

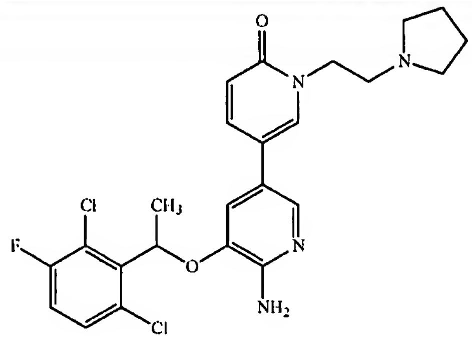
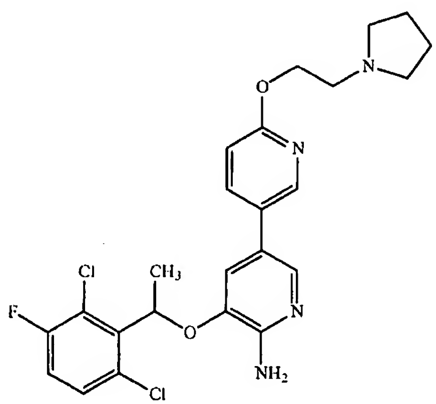
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-637		6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-(2-pyrrolidin-1-yl-ethyl)-1H-[3,3']-bipyridinyl-6-one	0.692	(400 MHz, DMSO-D6) d ppm 7.42–7.52(m, 2H) 7.25–7.35(m, 2H) 7.22(t, J=8.72 Hz, 1H) 6.64 (d, J=1.52 Hz, 1H) 6.19(d, J=9.35 Hz, 1H) 5.89 (q, J=6.74 Hz, 1H) 5.58(s, 2H) 3.72–3.84(m, 2H) 2.42–2.53(m, 2H) 1.57(d, J=6.57 Hz, 3H) 1.39–1.50(m, 4H)	491	35
I-638		5-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-pyrrolidin-1-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine	0.094	(400 MHz, DMSO-D6) d ppm 7.98(d, J=2.53 Hz, 1H) 7.62(d, J=2.02 Hz, 1H) 7.57(dd, J=8.59, 2.53 Hz, 1H) 7.40(dd, J=8.97, 4.93 Hz, 1H) 7.27(t, J=8.72 Hz, 1H) 6.77(d, J=1.77 Hz, 1H) 6.66(d, J=8.59 Hz, 1H) 5.97(q, J=6.57 Hz, 1H) 5.70(s, 2H) 4.17(t, J=5.81 Hz, 2H) 2.56–2.65 (m, 2H) 1.63(d, J=6.82 Hz, 3H) 1.46–1.54(m, 4H) 0.97–1.09(m, 1H)	491	35

TABLE 3-continued

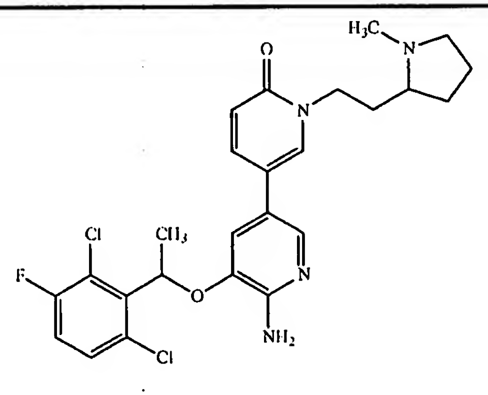
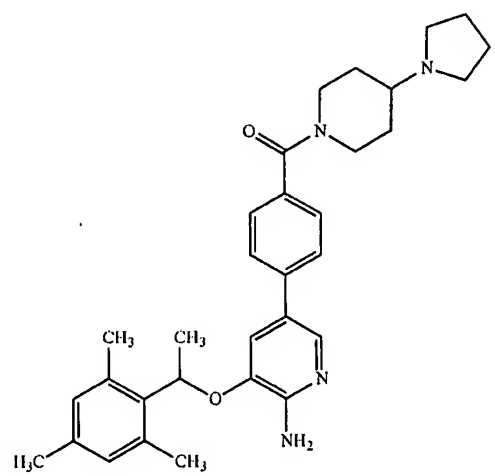
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
1-639		6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-1H-[3,3']bipyridinyl-6-one	0.513	(400 MHz, DMSO-D6) d ppm 7.71(dd, J=9.60, 1.77 Hz, 2H) 7.46-7.56(m, 2H) 7.42(t, J=8.72 Hz, 1H) 6.84(s, 1H) 6.39(d, J=9.35 Hz, 1H) 6.10(q, J=6.57 Hz, 1H) 5.79(s, 2H) 3.98-4.08 (m, 4H) 3.81-3.92(m, 2H) 2.85-2.92(m, 2H) 2.14-2.18(m, 7H) 1.93-2.05(m, 5H) 1.84-1.89(m, 2H) 1.76-1.82(m, 4H) 1.52-1.63(m, 6H) 1.26-1.38(m, 2H) 1.08-1.18(m, 6H)	505	3
1-640		(4-{6-Amino-5-[1-(2,4,6-trimethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		(400 MHz, MeOD) d ppm 7.62(d, J=1.52 Hz, 1H) 7.25-7.31(m, 2H) 7.19-7.25(m, 2H) 6.73 (s, 2H) 6.65(d, J=1.77 Hz, 1H) 5.65(q, J=6.57 Hz, 1H) 4.46-4.57(m, 1H) 3.61-3.73(m, 1H) 2.96-3.07(m, 1H) 2.73-2.84(m, 1H) 2.50-2.59 (m, 4H) 2.23-2.31(m, 7H) 2.10(s, 3H) 1.92-2.04 (m, 1H) 1.77-1.88(m, 1H) 1.69-1.76(m, 4H) 1.66(d, J=6.82 Hz, 3H) 1.29-1.40(m, 2H)	513	6

TABLE 3-continued

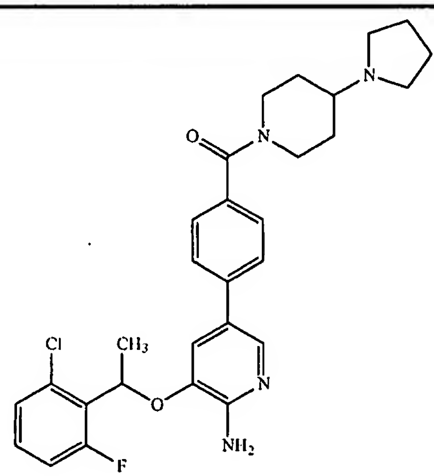
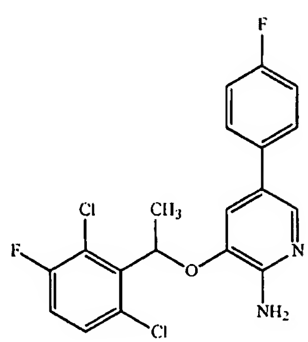
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-641		(4-{6-Amino-5-[1-(2-chloro-6-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		(400 MHz, McOD) d ppm 7.66(d, J=2.02 Hz, 1H) 7.28–7.39(m, 4H) 7.12–7.23(m, 2H) 7.07 (d, J=1.77 Hz, 1H) 6.92–7.02(m, 1H) 5.97(q, J=6.06 Hz, 1H) 4.44–4.56(m, 1H) 3.62–3.74 (m, 1H) 2.96–3.08(m, 1H) 2.72–2.84(m, 1H) 2.48–2.59(m, 4H) 2.20–2.31(m, 1H) 1.91–2.02 (m, 1H) 1.78–1.89(m, 1H) 1.66–1.77(m, 8H) 1.28–1.40(m, 2H)	523	6
I-642		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-phenyl)-pyridin-2-ylamine		(400 MHz, DMSO-D6) d ppm 7.61(d, J=1.77 Hz, 1H) 7.38(dd, J=8.97, 4.93 Hz, 1H) 7.20–7.29 (m, 3H) 6.99–7.07(m, 2H) 6.76(d, J=1.77 Hz, 1H) 5.95(q, J=6.65 Hz, 1H) 5.70(s, 2H) 1.62 (d, J=6.57 Hz, 3H)	395	1

TABLE 3-continued

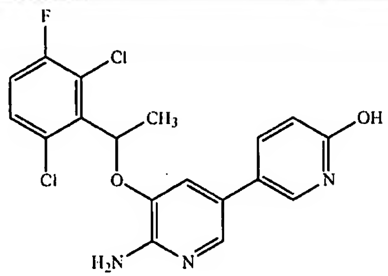
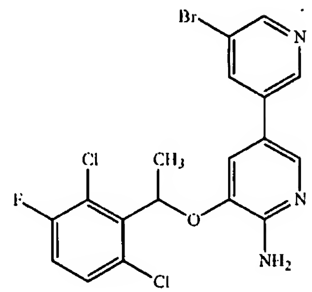
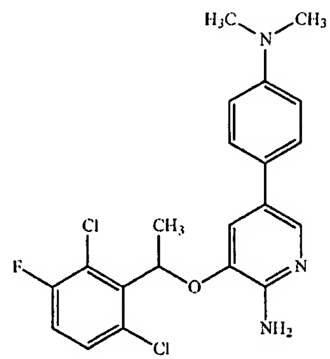
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-643		6'-Amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1H-[3,3']-bipyridinyl-6-one	0.0432	(500 MHz, DMSO-D6) d ppm 7.73(s, 1H) 7.73–7.46(m, 5H) 7.09(d, J=1.55 Hz, 1H) 6.42(d, J=9.5 Hz, 1H) 6.29(q, J=6.65 Hz, 1H) 1.84(d, J=6.60 Hz, 3H)	394	3
I-644		5'-Bromo-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine	0.1958	(300 MHz, CDCl3-D1) d ppm 8.54(d, 2H) 7.80 (m, 2H) 7.33(m, 1H) 7.08(m, 1H) 6.93(s, 1H) 6.12(q, J=6.7 Hz, 1H) 5.041(br. s, 2H) 1.88 (d, J=6.7 Hz, 3H)	458 [M+2]	3
I-645		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-dimethylamino-phenyl)-pyridin-2-ylamine	0.1572	(300 MHz, CDCl3-D1) d ppm 7.83(d, J=1.87 Hz, 1H) 7.28(m, 4H) 7.04(m, 1H) 6.98(d, J=1.76 Hz, 1H) 6.75(m, 2H) 6.11(q, J=6.7 Hz, 1H) 4.76 (br. s, 2H) 2.97(s, 6H) 1.85(d, J=6.7Hz, 3H)	420	3

TABLE 3-continued

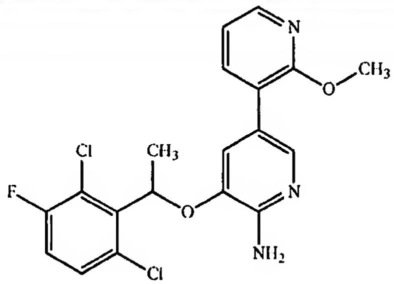
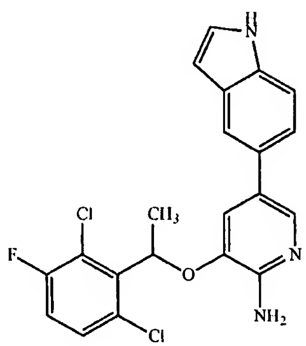
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-646		5-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-2'-methoxy-[3,3']bipyridinyl-6-ylamine	0.099	(300 MHz, CDCl3-D1) d ppm 8.10(s, 1H) 7.77 (s, 1H) 7.50(m, 1H) 7.30(m, 1H) 7.09(m, 2H) 6.92(m, 1H) 6.06(d, J=6.7 Hz, 1H) 4.91(br. s, 2H) 3.87(s, 3H) 1.83(d, J=6.7 Hz, 3H)	MS408 m/z	3
I-647		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-indol-5-yl)-pyridin-2-ylamine	0.1664	(300 MHz, CDCl3-D1) d ppm 8.21(s, 1H) 7.93 (m, 1H) 7.64(m, 1H) 7.43(m, 1H) 7.32–7.21 (m, 3H) 7.09–7.024(m, 2H) 6.58(m, 1H) 6.16 (m, 1H) 4.80(s, 2H) 3.50(s, 2H) 1.87(d, J=6.69 Hz, 3H)	416	3

TABLE 3-continued

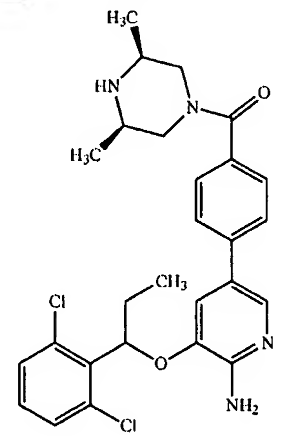
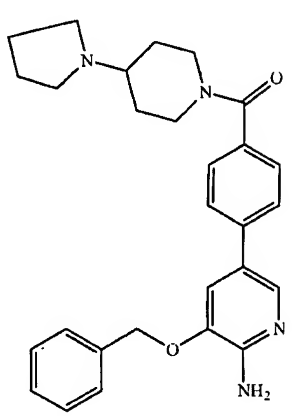
No.	Structure	Name	Ki (µM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-648		(4-{6-Amino-5-[1-(2,6-dichloro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone	0.5533	(300 MHz, CDCl3-D1) d ppm 7.87(s, 1H) 7.42 (m, 4H) 7.30(m, 3H) 7.16(m, 1H) 7.05(s, 1H) 5.92(m, 1H) 4.97(s, 2H) 4.61(br. s, 1H) 3.65 (br. s, 2H) 2.85(br. s, 3H) 2.49(br. s, 1H) 2.41 (m, 3H) 2.19(m, 1H) 1.08(m, 6H)	513	1
I-649		[4-(6-Amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	29%	(400 MHz, DMSO-D6) d ppm 7.92(d, J=1.77 Hz, 1H) 7.68(d, J=8.34 Hz, 2H) 7.53(d, J=7.07 Hz, 2H) 7.37-7.46(m, 5H) 7.33(m, 1H) 5.96(s, 2H) 5.25(s, 2H) 3.49(s, 2H) 3.09(s, 2H) 2.00 (s, 2H) 1.84(s, 2H) 1.56(s, 1H)	457	1

TABLE 3-continued

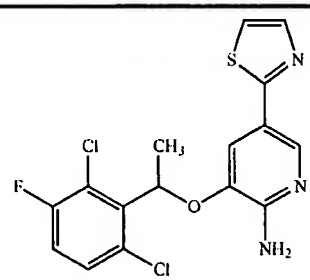
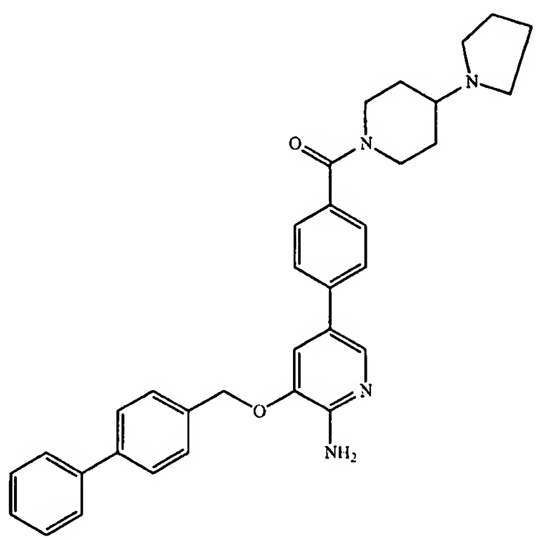
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-650		3-(2,6-Dichloro-3-fluoro-benzyloxy)-5-thiazol-2-yl-pyridin-2-ylamine	0.3627	(300 MHz, CDCl3-D1) d ppm 8.25(d, J=1.79 Hz, 1H) 7.76(d, J=3.30 Hz) 7.36–7.26(m, 3H) 7.20(m, 1H) 7.05(m, 1H) 6.17(q, J=6.7 Hz, 1H) 5.09(br. s, 2H) 1.86(d, J=6.7 Hz, 3H)	384	37
I-651		(4-{6-Amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	1.5258	(400 MHz, DMSO-D6) d ppm 7.93(d, J=1.52 Hz, 1H) 7.74–7.82(m, 3H) 7.71 m, 3H) 7.62–7.67 (m, 3H) 7.47(m, 4H) 7.38(m, 1H) 5.43(s, 2H) 3.67(br. s, 2H) 3.51(br. s, 3H) 3.40(br. s, 1H) 3.09(br. s, 2H) 2.00(br. s, 3H) 1.83(br. s, 2H) 1.53(br. s, 2H)	533	6

TABLE 3-continued

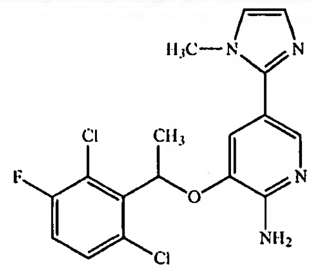
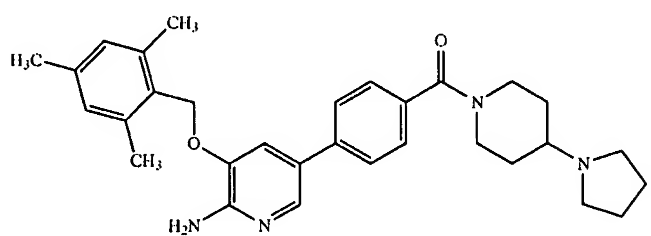
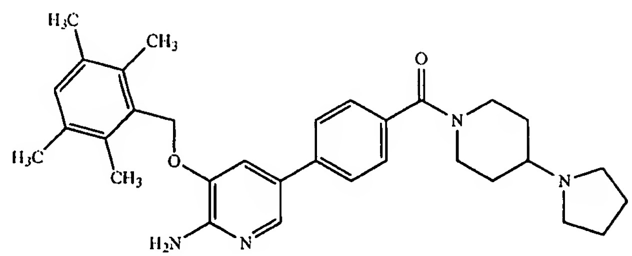
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-652		3-(2,6-Dichloro-3-fluoro-benzyloxy)-5-(1-methyl-1H-imidazol-2-yl)-pyridin-2-ylamine	11%	(300 MHz, CDCl3-D1) d ppm 7.90(d, J=1.67 Hz, 1H) 7.30(m, 2H) 7.05(m, 3H) 6.91(d, J=0.98 Hz, 1H) 6.10(q, J=6.7 Hz, 1H) 4.99(br. s, 2H) 3.57(s, 3H) 1.83(d, J=6.7 Hz, 3H)	381	38
I-653		{4-[6-Amino-5-(2,4,6-trimethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	2%	(400 MHz, DMSO-D6) d ppm 7.92(s, 1H) 7.90 (s, 1H) 7.84(d, J=8.34 Hz, 2H) 7.50(d, J=8.34 Hz, 2H) 6.92(s, 2H) 5.27(s, 2H) 3.51(br. s, 8H) 3.09(br. s, 3H) 2.32(s, 6H) 2.25(s, 3H) 1.99(br. s, 2H) 1.84(br. s, 2H) 1.55(br. s, 2H)	499	6
I-654		{4-[6-Amino-5-(2,3,5,6-tetramethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	9%	(400 MHz, DMSO-D6) d ppm 9.75(s, 1H) 7.88 (s, 2H) 7.79(d, J=8.34 Hz, 2H) 7.45(d, J=8.08 Hz, 3H) 6.97(s, 1H) 5.28(s, 2H) 3.64(s, 1H) 3.45(s, 2H) 3.34(s, 1H) 3.04(s, 3H) 2.15(s, 12H) 1.94(s, 3H) 1.79(s, 2H) 1.50(s, 2H)	513	6

TABLE 3-continued

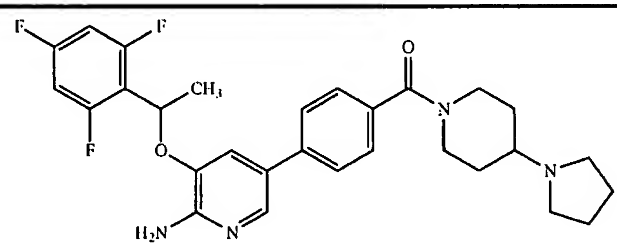
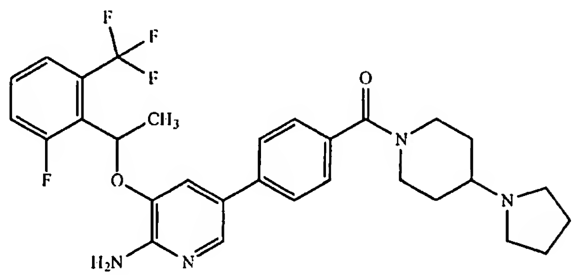
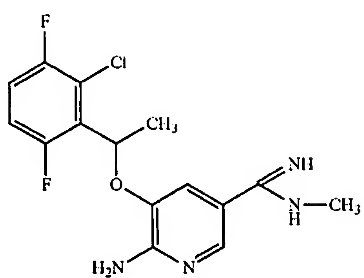
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-655		{4-[6-Amino-5-(2,4,6-trifluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		(400 MHz, DMSO-D6) d ppm 7.83(d, J=2.02 Hz, 1H) 7.48(d, J=8.34 Hz, 3H) 7.33(d, J=8.34 Hz, 3H) 7.24(d, J=1.77 Hz, 1H) 7.12–7.22 (m, 2H) 5.86(m, 1H) 5.76(s, 2H) 4.19(br. s, 1H) 3.55 (br. s, 1H) 2.96(br. s, 2H) 2.16(br. s, 1H) 1.83 (br. s, 2H) 1.69(br. s, 5H) 1.60(d, J=5.67 Hz, 5H) 1.30(br. s, 2H)	525	6
I-656		(4-{6-Amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		(400 MHz, DMSO-D6) d ppm 7.89(d, J=1.77 Hz, 1H) 7.57–7.66(m, 3H) 7.41–7.49(m, 2H) 7.36(d, J=8.08 Hz, 2H) 7.19(d, J=1.77 Hz, 1H) 5.85(s, 2H) 5.80(s, 1H) 4.21(s, 1H) 3.57(br. s, 1H) 3.02(s, 2H) 2.22(s, 1H) 1.80(br. s, 2H) 1.78(d, J=6.3 Hz, 3H) 1.66(s, 4H) 1.34(s, 2H)	557	6
I-657		6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-methyl-nicotinamidine		(400 MHz, DMSO-D6) δ ppm 8.82(br. s, 1H) 7.97(d, J=1.77 Hz, 1H) 7.52–7.57(m, 1H) 7.46(t, J=8.72 Hz, 1H) 7.05(d, J=1.26 Hz, 1H) 6.73(br. s, 1H) 6.06(quart., J=6.57 Hz, 1H) 2.91(s, 3H) 1.78(d, J=6.57 Hz, 3H)	357	39

TABLE 3-continued

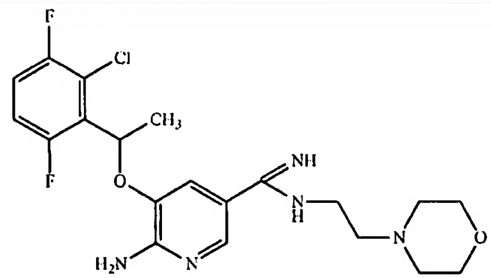
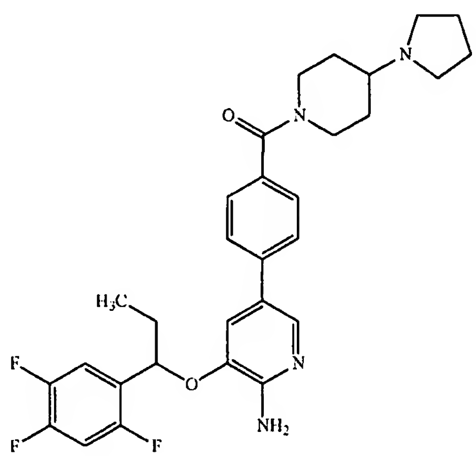
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-658		6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-(2-morpholin-4-yl-ethyl)-nicotinamidine		(400 MHz, DMSO-D6) δ ppm 9.07(br. s, 1H) 7.94(d, J=1.52 Hz, 1H) 7.53(m, 1H) 7.47 (m, 1H) 6.97(s, 1H) 6.77(br. s, 1H) 6.06(s, 1H) 3.55(quart, J=4.29 Hz, 2H) 3.54(m, 2H) 3.47 (m, 2H) 2.54(t, J=6.06 Hz, 2H) 2.42(s, 3H) 1.78(d, J=6.82 Hz, 3H)	456	39
I-659		(4-{6-Amino-5-[1-(2,4,5-trifluoro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		(400 MHz, DMSO-D6) d ppm 9.84(s, 1H) 7.91 (d, J=1.52 Hz, 1H) 7.78–7.88(m, 1H) 7.65–7.75(m, 3H) 7.57(dd, J=10.23, 3.66 Hz, 1H) 7.46(d, J=8.34 Hz, 2H) 5.91–5.98(m, 1H) 3.50 (s, 2H) 3.40(s, 1H) 3.09(s, 2H) 2.09(dt, J=14.08, 6.98 Hz, 2H) 1.99(s, 2H) 1.92(dt, J=13.90, 6.95 Hz, 2H) 1.83(s, 2H) 1.55(s, 2H) 0.92(t, J=7.33 Hz, 3H)	540	6

TABLE 3-continued

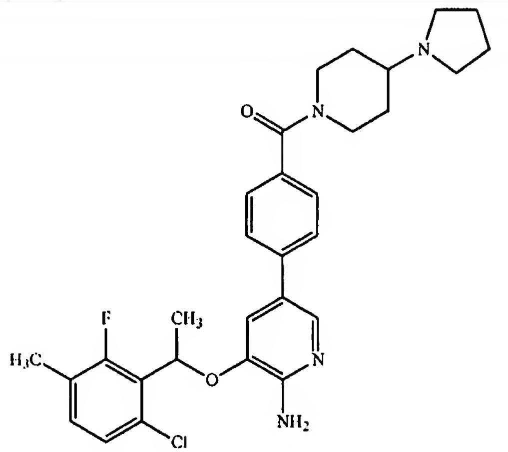
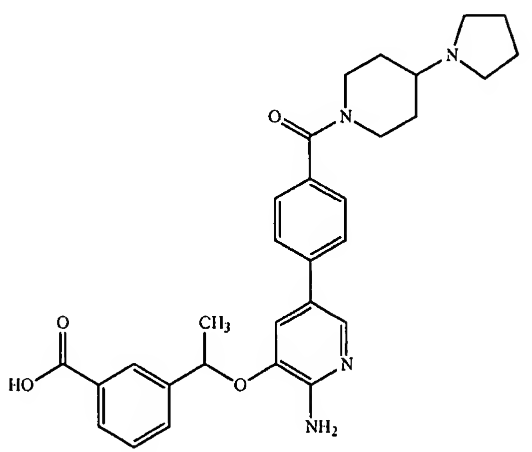
No.	Structure	Name	Ki (μM) or I (%)	^{1}H-NMR	MS m/z (M + H)	Procedure
I-660		(4-{6-Amino-5-[1-(6-chloro-2-fluoro-3-methyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		NMR (400 MHz, DMSO-D6) d ppm 9.84(s, 1H) 7.95(s, 2H) 7.65(d, J=8.34 Hz, 2H) 7.53–7.60(m, 2H) 7.48(s, 1H) 7.32–7.42(m, 2H) 6.25(q, J=6.48 Hz, 1H) 3.58(s, 2H) 3.49(s, 1H) 3.18(d, J=5.05 Hz, 3H) 2.27(d, J=1.52 Hz, 5H) 2.01–2.13(m, 4H) 1.89(d, J=6.57 Hz, 5H) 1.64(s, 2H)	539	6
I-661		3-(1-{2-Amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-benzoic acid		(400 MHz, DMSO-D6) d ppm10.14(s, 1H) 8.12 (s, 1H) 7.93(s, 1H) 7.76–7.87(m, 4H) 7.72(s, 1H) 7.65(d, J=8.34 Hz, 2H) 7.53(ddd, J=15.92, 7.83, 7.58 Hz, 2H) 7.40–7.47(m, 3H) 6.03–6.10(m, 1H) 4.55(s, 1H) 3.64(s, 1H) 3.47(s, 2H) 3.38(s, 1H) 3.07(s, 3H) 2.13(s, 1H) 1.98 (s, 3H) 1.78–1.89(m, 3H) 1.65(t, J=5.68 Hz, 3H) 1.56(s, 2H) 1.31(d, J=6.57 Hz, 2H)	516	6

TABLE 4

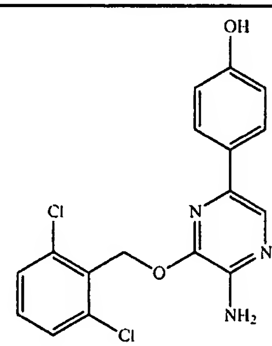
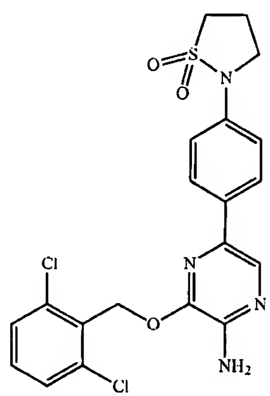
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-1		4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenol	1.35	see examples	(400 MHz, DMSO-d_6) δ 5.61(s, 2H), 6.09(s, 2H), 6.79(d, 2H), 7.45(t, 1H), 2.56(d, 2H), 7.76(d, 2H), 7.99(s, 1H), 9.46(s, 1H)	362
II-2		3-(2,6-Dichloro-benzyloxy)-5-[4-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-pyrazin-2-ylamine	0.825	see examples	(400 MHz, DMSO-d_6) δ 2.41(m, 2H), 3.51(m, 2H), 3.76(m, 2H), 5.62(s, 2H), 6.28(s, 2H), 7.22 (m, 2H), 7.48(m, 1H), 7.56(m, 2H), 7.94(m, 2H), 8.14(s, 1H)	465

TABLE 4-continued

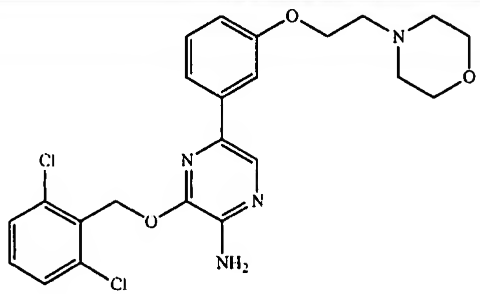
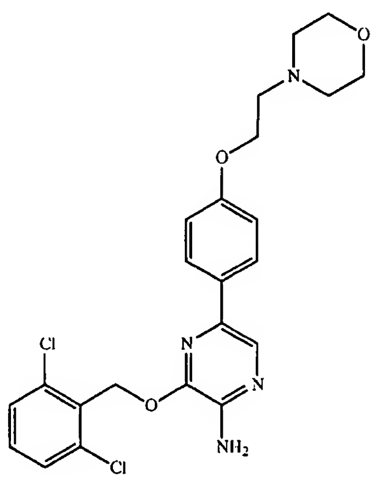
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-3		3-(2,6-Dichloro-benzyloxy)-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine	0.74	see examples	(400 MHz, DMSO-d_6) δ 2.45(m, 4H), 2.71(t, 2H), 3.56(t, 4H), 4.15(t, 2H), 5.61(s, 2H), 6.32 (s, 2H), 6.86(d, 1H), 7.29(t, 1H), 7.46(m, 2H), 7.52(m, 1), 7.55(s, 1H), 7.57(d, 1H), 8.16(s, 1H)	475
II-4		3-(2,6-Dichloro-benzyloxy)-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine	1.25	see examples	(400 MHz, DMSO-d_6) δ 2.45(m, 4H), 2.71(m, 2H), 3.59(t, 4H), 4.11(t, 2H), 5.64(s, 2H), 6.18 (s, 2H), 6.97(d, 2H), 7.46(t, 1H), 7.56(d, 2H), 7.86(d, 2H), 8.06(s, 1H)	475

TABLE 4-continued

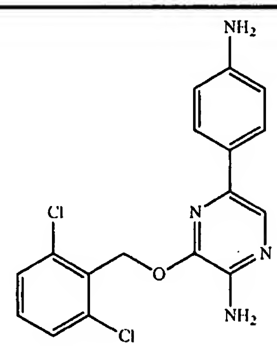
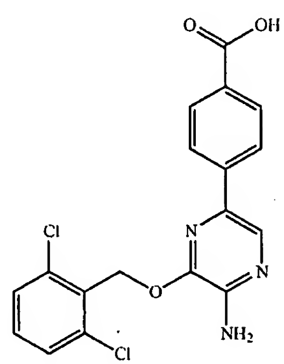
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-5		5-(4-Amino-phenyl)-3-(2,6-dichloro-benzyloxy)-pyrazin-2-ylamine	0.94	see examples	(400 MHz, DMSO-d_6) δ 5.19(s, 2H), 5.59(s, 2H), 5.96(s, 2H), 6.60(d, 2H), 7.45(t, 1H), 7.56(d, 2H), 7.62(d, 2H), 7.91(s, 1H)	361
II-6		4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-benzoic acid	1.75	see examples	(400 MHz, DMSO-d_6) δ 5.64(s, 2H), 6.52(s, 2H), 7.46(m, 1H), 7.56(m, 2H), 7.96(d, 2H), 8.07(d, 2H), 8.27(s, 1H)	390

TABLE 4-continued

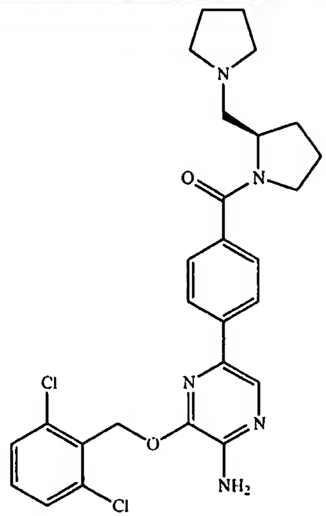
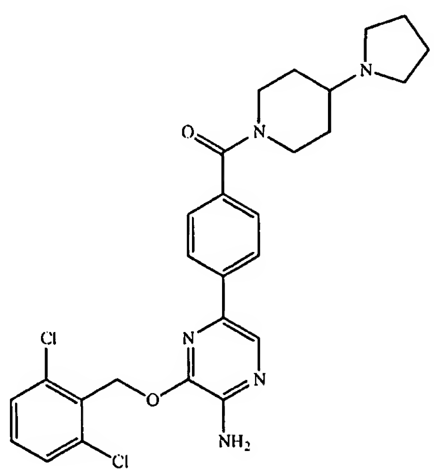
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-7		{4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.24	see examples	(400 MHz, DMSO-d_6) δ 1.79(m, 10H), 2.64(m, 4H), 3.45(m, 3H), 5.64(s, 2H), 6.42(s, 2H), 7.49 (m, 3H), 7.58(m, 2H), 7.98(d, 2H), 8.00(s, 1H)	526
II-8		{4-[5-Amino-6-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.56	see examples	(400 MHz, DMSO-d_6) δ 1.37(m, 2H), 1.66(m, 4H), 1.85(m, 2H), 2.32(m, 2H), 2.52(m, 4H), 3.04(m, 2H), 3.92(m, 1H), 5.62(s, 2H), 6.42(s, 2H), 7.40(d, 2H), 7.46(t, 1H), 7.58(m, 2H), 8.00 (d, 2H), 8.21(s, 1H)	526

TABLE 4-continued

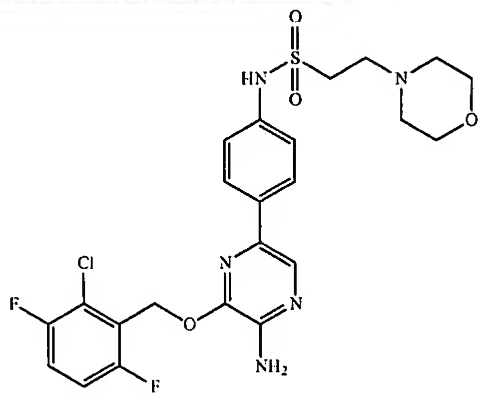
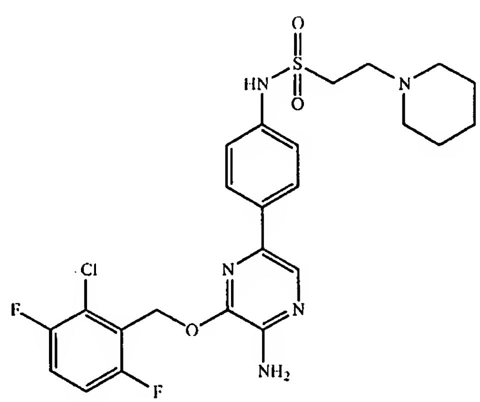
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-9		2-Morpholin-4-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.26	see examples	(300 MHz, $CDCl_3$) δ 2.50(t, 4H), 2.92(t, 2H), 3.29(t, 2H), 3.72(t, 2H), 4.81(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.28(d, 2H), 7.90(d, 2H), 8.04(s, 1H)	540
II-10		2-Piperidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.2	see examples	(300 MHz, $CDCl_3$) δ 1.60(m, 2H), 1.63(m, 4H), 2.49(m, 4H), 2.90(t, 2H), 3.26(t, 2H), 4.85(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.29(d, 2H), 7.89(d, 2H), 8.04(s, 1H)	538

TABLE 4-continued

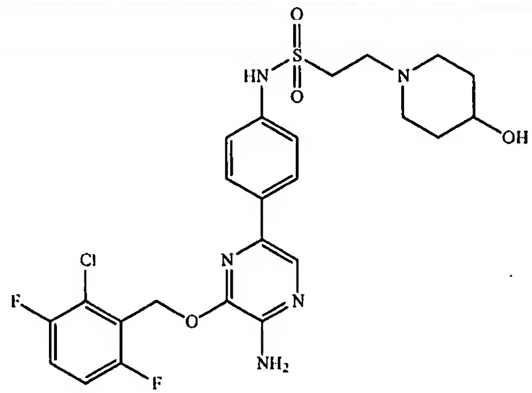
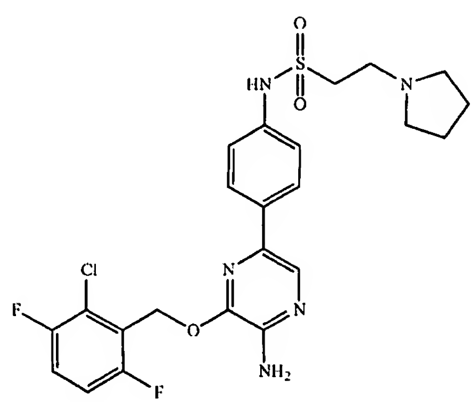
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-11		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.65	see examples	(300 MHz, $CDCl_3$) δ 1.63(m, 2H), 1.90(m, 2H), 2.27(t, 2H), 2.80(m, 2H), 2.92(t, 2H), 4.86(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.28(d, 2H), 7.90(d, 2H), 8.04(s, 1H)	554
II-12		2-Pyrrolidin-1-yl-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.58	see examples	(300 MHz, $CDCl_3$) δ 1.83(m, 4H), 2.56(m, 4H), 3.04(t, 2H), 3.28(t, 2H), 4.91(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.27(d, 2H), 7.88(d, 2H), 8.03(s, 1H)	524

TABLE 4-continued

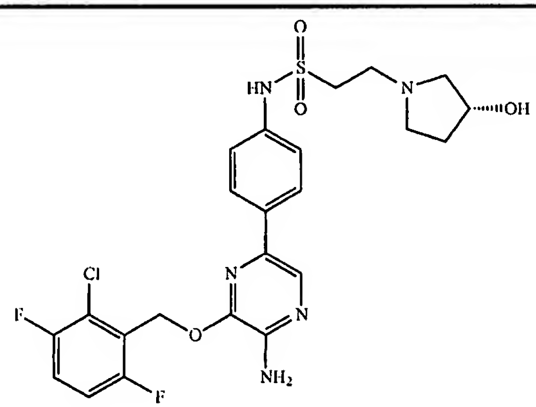
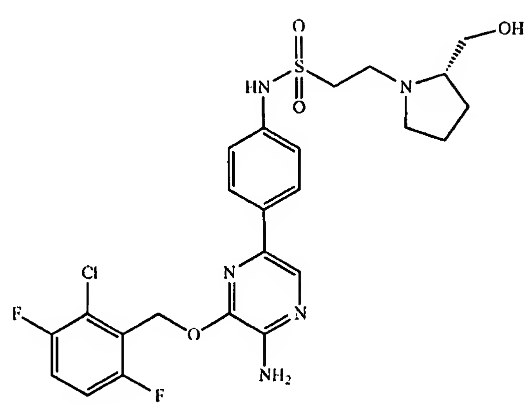
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-13		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.59	see examples	(300 MHz, $CDCl_3$) δ 1.85(m, 1H), 2.25(m, 2H), 2.55(m, 1H), 2.84(d, 1H), 3.02(m, 3H), 3.26(m, 2H), 4.43(m, 1H), 4.82(s, 2H), 5.67(d, 2H), 7.05 (m, 1H), 7.20(m, 1H), 7.35(d, 2H), 7.88(d, 2H), 8.04(s, 1H)	540
II-14		2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.78	see examples	(300 MHz, $CDCl_3$) δ 1.85(m, 4H), 2.20(m, 1H), 2.70(m, 2H), 3.05(m, 2H), 3.30-3.70(m, 3H), 3.95(m, 1H), 4.79(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.32(d, 2H), 7.88(d, 2H), 8.05 (s, 1H)	554

TABLE 4-continued

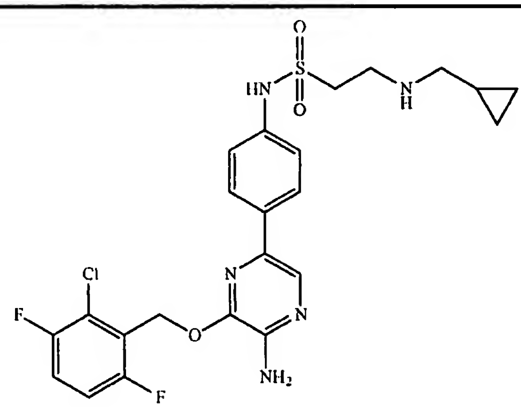
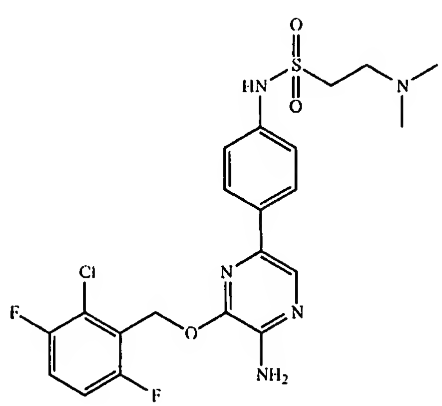
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-15		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.28	see examples	^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14(m, 2H), 0.52 (m, 2H), 0.95(m, 1H), 2.50(d, 2H), 3.21(m, 4H), 4.86(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.30(d, 2H), 7.89(d, 2H), 8.04(s, 1H)	524
II-16		2-Dimethylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.91	see examples	(300 MHz, $CDCl_3$) δ 2.30(s, 6H), 2.86(t, 2H), 3.21(t, 2H), 4.83(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.18(m, 1H), 7.28(d, 2H), 7.88(d, 2H), 8.05 (s, 1H)	498

TABLE 4-continued

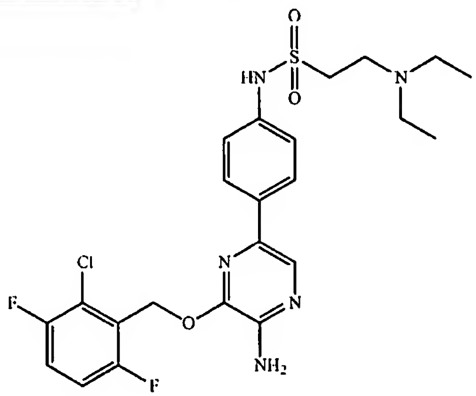
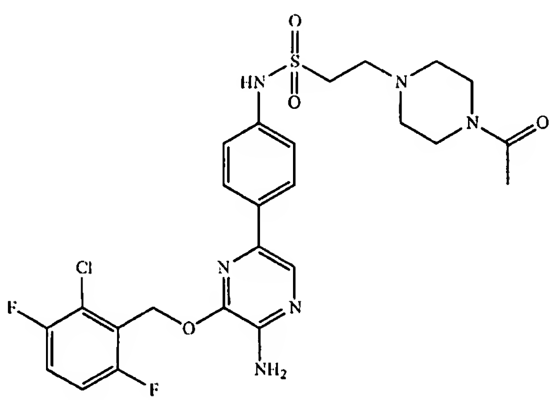
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-17		2-Diethylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.46	see examples	(300 MHz, $CDCl_3$) δ 1.08(t, 6H), 2.61(q, 4H), 3.03(t, 2H), 3.23(t, 2H), 4.80(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.19(m, 1H), 7.27(d, 2H), 7.88(d, 2H), 8.04(s, 1H)	526
II-18		2-(4-Acetyl-piperazin-1-yl)-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.5	see examples	(300 MHz, $CDCl_3$) δ 2.08(s, 3H), 2.46(m, 4H), 2.93(t, 2H), 3.30(t, 2H), 3.47(t, 2H), 3.62(t, 2H), 4.82(s, 2H), 5.67(s, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.28(d, 2H), 7.91(d, 2H), 8.05(s, 1H)	581

TABLE 4-continued

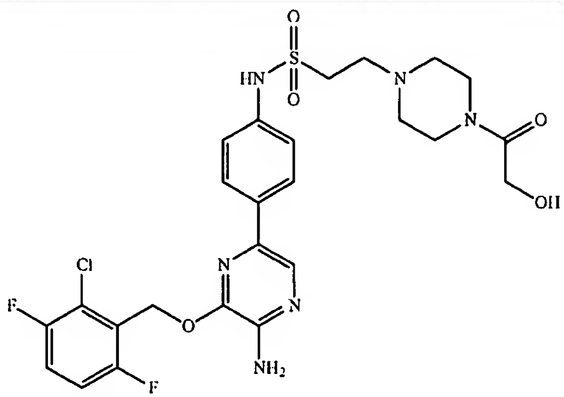
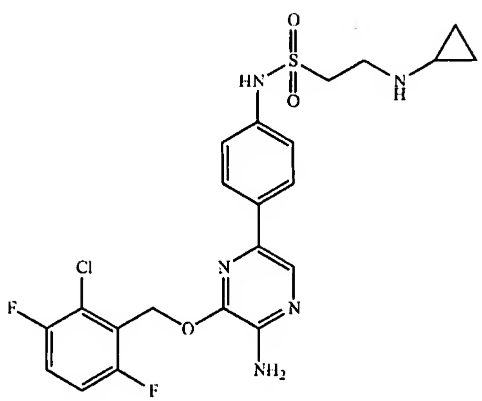
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-19		2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.45	see examples	(300 MHz, $CDCl_3$) δ 2.48(t, 4H), 2.93(t, 2H), 3.30(m, 4H), 3.55(brs, 1H), 3.67(t, 2H), 4.14(s, 2H), 4.84(s, 2H), 5.67(s, 2H), 7.05(m, 1H), 7.20 (m, 1H), 7.27(d, 2H), 7.92(d, 2H), 8.05(s, 1H)	597
II-20		2-Cyclopropylamino-ethanesulfonic acid {4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.29	see examples	(300 MHz, $CDCl_3$) δ 0.37(m, 2H), 0.49(m, 2H), 2.14(m, 1H), 3.24(m, 4H), 4.93(s, 2H), 5.67(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.28(d, 2H), 7.90(d, 2H), 8.03(s, 1H)	510

TABLE 4-continued

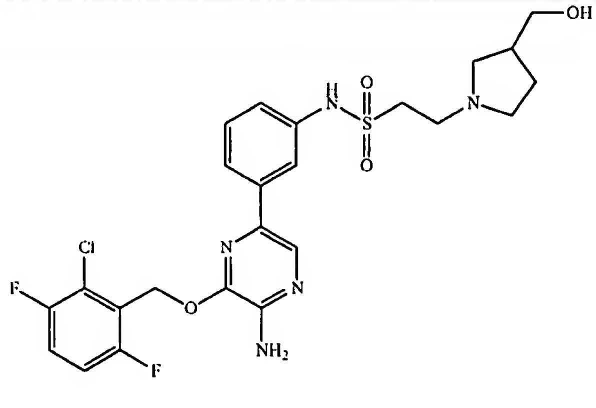
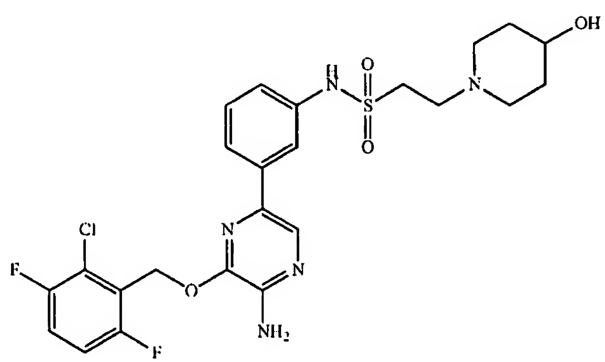
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-21		2-[(3R)-3-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.38	see examples	(300 MHz, $CDCl_3$) δ 1.60–2.0(m, 5H), 2.15 (m, 1H), 2.55–2.70(m, 2H), 2.90–3.15(m, 2H), 3.3–3.62(m, 2H), 3.89(dd, J=3.0, 11.3 Hz, 1H), 4.92(s, 2H), 5.66(s, 2H), 6.95–7.60(m, 5H), 7.55–7.70(m, 2H), 7.77(s, 1H), 8.10(s, 1H)	554
II-22		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	0.7	see examples	(300 MHz, $CDCl_3$) δ 1.40–1.60(m, 2H), 1.75–1.88 (m, 2H), 2.21(t, J=9.0 Hz, 2H), 2.65–2.75 (m, 2H), 2.85–2.95(m, 2H), 3.20–3.35(m, 2H), 3.69 (m, 1H), 5.17(s, 2H), 5.68(s, 2H), 6.92–7.02(m, 1H), 7.08–7.20(m, 1H), 7.30–7.45(m, 2H), 7.69 (s, 1H), 7.76(d, J=7.5 Hz, 1H), 8.14(s, 1H)	555

TABLE 4-continued

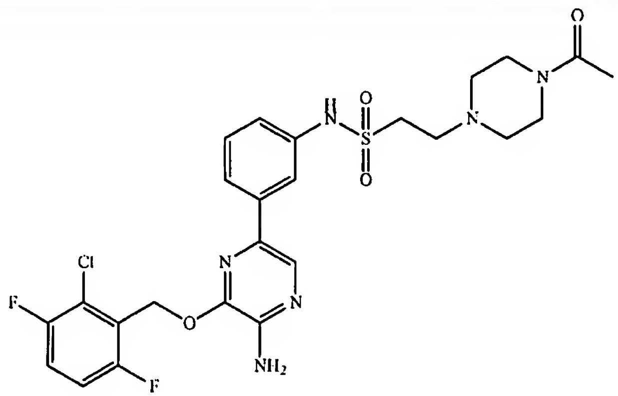
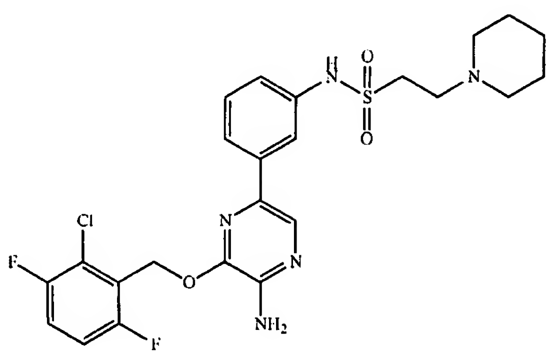
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-23		2-(4-Acetyl-piperazin-1-yl)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl]-amide	2.79	see examples	(300 MHz, $CDCl_3$) δ 2.03(s, 3H), 2.30–2.40(m, 2H), 2.75–2.85(m, 2H), 3.20–3.40(m, 4H), 3.45–3.55(m, 2H), 5.35(s, 2H), 5.68(s, 2H), 6.95–7.02 (m, 1H), 7.05–7.20(m, 1H), 7.30–7.45(m, 2H), 7.64(s, 1H), 7.76(d, J=7.3 Hz, 1H), 8.13(s, 1H), 8.52(s, 1H)	582
II-24		2-Piperidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	3.5	see examples	(300 MHz, $CDCl_3$) δ 1.30–1.60(m, 6H), 2.30–2.45 (m, 4H), 2.75–2.90(m, 2H), 3.15–3.30(m, 2H), 5.10(s, 2H), 5.66(s, 2H), 6.95–7.05(m, 1H), 7.10–7.20(m, 1H), 7.25–7.40(m, 2H), 7.60–7.75(m, 2H), 8.10(s, 1H)	539

TABLE 4-continued

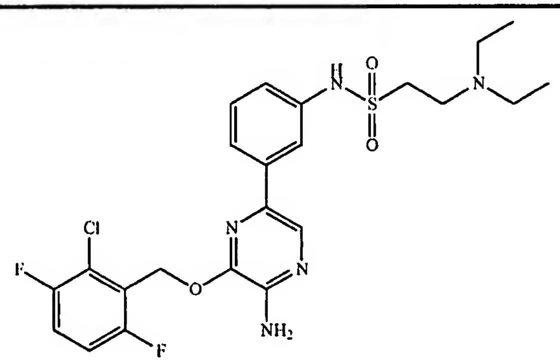
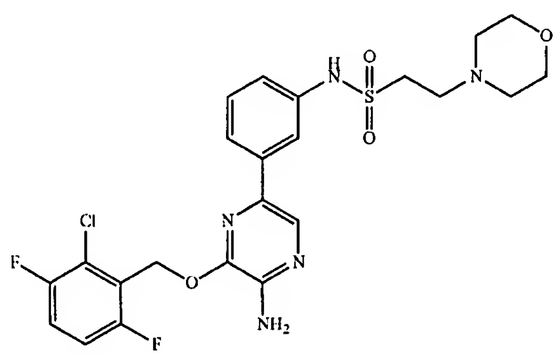
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-25		2-Diethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	3.7	see examples	(300 MHz, $CDCl_3$) δ 0.95–1.05(m, 6H), 2.45–2.55 (m, 4H), 2.95–3.10(m, 2H), 3.15–3.25(m, 2H), 5.11(s, 2H), 5.67(s, 2H), 6.90–7.15(m, 2H), 7.20–7.40(m, 2H), 7.55–7.70(m, 2H), 8.10(s, 1H)	527
II-26		2-Morpholin-4-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	3.3	see examples	(300 MHz, $CDCl_3$) δ 2.30–2.50(m, 2H), 2.80–3.00 (m, 2H), 3.20–3.40(m, 2H), 3.50–3.75(m, 4H), 5.21(s, 2H), 5.67(s, 2H), 6.95–7.08(m, 1H), 7.10–7.20(m, 1H), 7.30–7.50(m, 2H), 7.67(s, 1H), 7.74(d, J=7.5 Hz, 1H), 8.12(s, 1H)	541

TABLE 4-continued

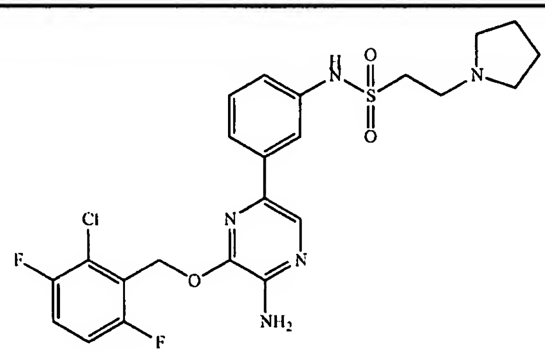
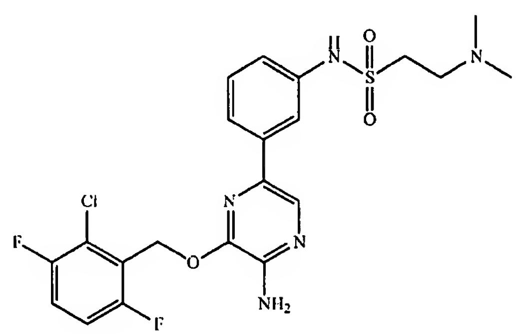
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-27		2-Pyrrolidin-1-yl-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.8	see examples	(300 MHz, $CDCl_3$) δ 1.62–1.82(m, 4H), 2.40–2.55 (m, 4H), 2.92–3.00(m, 2H), 3.25–3.35 (m, 2H), 5.24(s, 2H), 5.67(s, 2H), 6.95–7.08(m, 1H), 7.10–7.20(m, 1H), 7.25–7.40(m, 2H), 7.63(s, 1H), 7.73(d, J=7.1 Hz, 1H), 8.12(s, 1H)	525
II-28		2-Dimethylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	2.28	see examples	(300 MHz, $CDCl_3$) δ 2.27(s, 6H), 2.86(t, J=6.4 Hz, 2H), 3.23(t, J=6.4 Hz, 2H), 5.08(s, 2H), 5.67(s, 2H), 7.00–7.45(m, 4H), 7.65–7.75(m, 2H), 8.11(s, 1H)	499

TABLE 4-continued

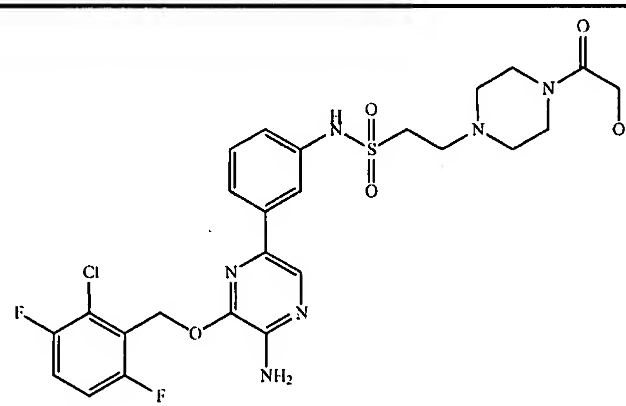
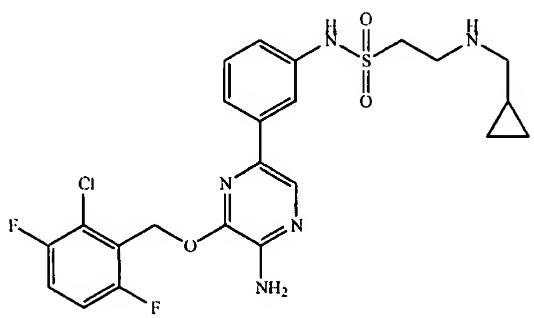
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-29		2-[4-(2-Hydroxy-acetyl)-piperizin-1-yl]-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.82	see examples	(300 MHz, $CDCl_3$) δ 2.43(t, 4H), 2.92(t, 2H), 3.20(t, 2H), 3.33(t, 2H), 3.54(br s, 1H), 3.61(t, 2H), 4.08(s, 2H), 5.18(br s, 2H), 5.67(s, 2H), 7.00–7.45(m, 4H), 7.65–7.75(m, 2H), 8.11(s, 1H)	597
II-30		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	1.84	see examples	(300 MHz, $CDCl_3$) δ 0.07(m, 2H), 0.44(m, 2H), 0.89(m, 1H), 2.45(d, 2H), 3.16(t, 2H), 3.29 (t, 2H), 5.27(br s, 2H), 5.67(s, 2H), 7.07(m, 1H), 7.20(m, 1H), 7.41(m, 2H), 7.65(s, 1H), 7.77(m, 1H), 8.12(s, 1H)	524

TABLE 4-continued

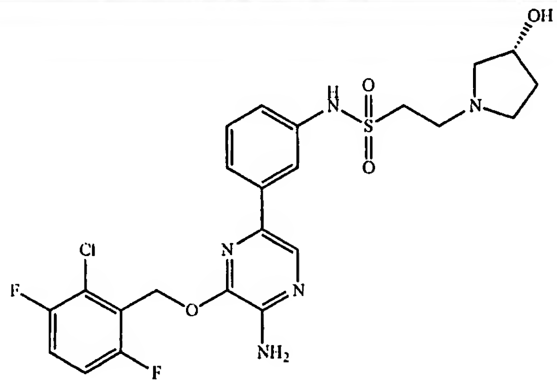
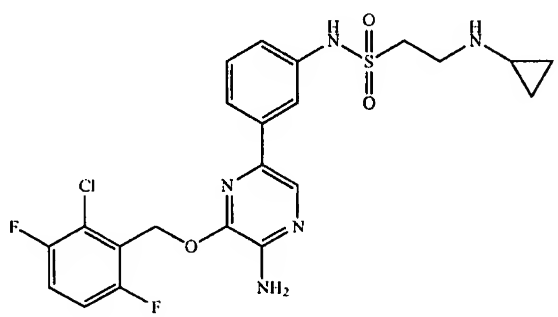
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-31		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	2.16	see examples	(300 MHz, $CDCl_3$) δ 1.80(m, 1H), 2.20(m, 2H), 2.50(m, 1H), 2.70-3.20(m, 5H), 3.32(m, 2H), 4.35(m, 1H), 5.12(s, 2H), 5.68(s, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.40(m, 2H), 7.73(m, 2H), 8.15(s, 1H)	540
II-32		2-Cyclopropylamino-ethanesulfonic acid {3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-amide	2.13	see examples	(300 MHz, $CDCl_3$) δ 0.25–0.50(m, 4H), 2.09(m, 1H), 3.15–3.40(m, 4H), 5.37(s, 2H), 5.68(s, 2H), 7.07(m, 1H), 7.18(m, 1H), 7.42(m, 2H), 7.62 (m, 1H), 7.77(m, 1H), 8.13(s, 1H)	510

TABLE 4-continued

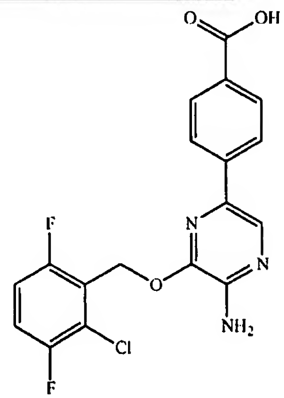
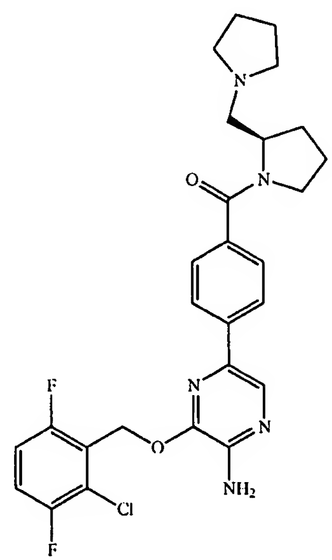
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-33		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid		see examples		392
II-34		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.15	see examples	(300 MHz, $CDCl_3$) δ 1.5–2.2(m, 10H), 2.65(m, 4H), 3.50(m, 2H), 4.42(m, 1H), 4.86(br s, 2H), 5.68(d, J=1.3 Hz, 2H), 7.05(m, 1H), 7.19(m, 1H), 7.57(m, 2H), 7.96(d, 2H), 8.12(s, 1H)	528

TABLE 4-continued

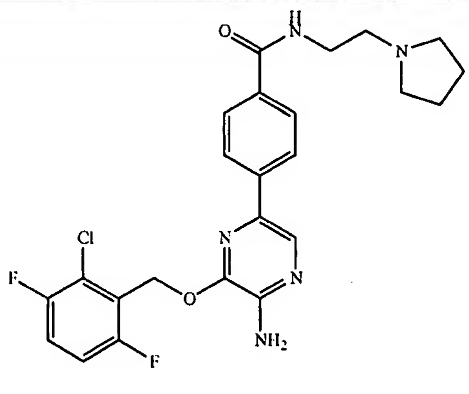
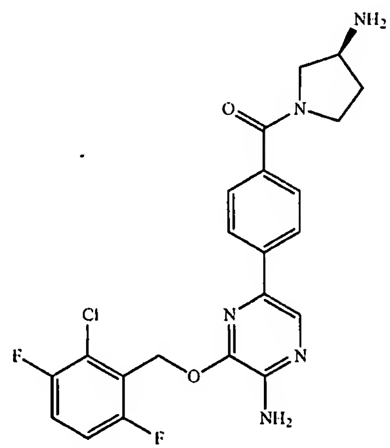
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-35		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.13	see examples	(300 MHz, $CDCl_3$) δ 1.87(m, 4H), 2.73(m, 4H), 2.85(t, 2H), 3.64(m, 2H), 4.91(s, 2H), 5.68(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.89(d, 2H), 7.99(d, 2H), 8.13(s, 1H)	489
II-36		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	0.37	see examples	(300 MHz, $CDCl_3$) δ 1.80–2.40(m, 2H), 2.24(s, 3H), 3.30–3.90(m, 5H), 5.71(s, 2H), 7.25(m, 1H), 7.35(m, 1H), 7.60(m, 2H), 8.03(d, 2H), 8.10(s, 1H)	461

TABLE 4-continued

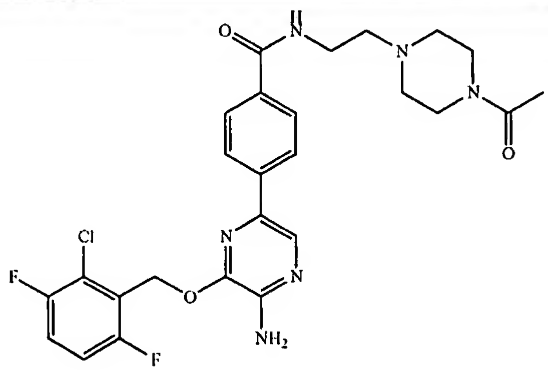
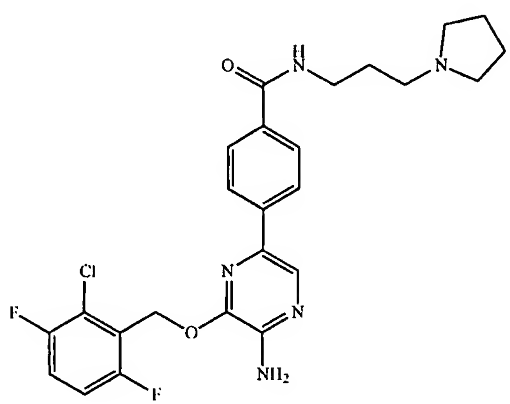
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-37		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide	1.35	see examples	(300 MHz, $CDCl_3$) δ 2.10(s, 3H), 2.52(m, 4H), 2.66(t, 2H), 3.40-3.80(m, 6H), 4.94(s, 2H), 5.68 (s, 2H), 6.75(brs, 1H), 7.05(m, 1H), 7.20(m, 1H), 7.84(d, 2H), 8.00(d, 2H), 8.14(s, 1H)	545
II-38		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.58	see examples	(300 MHz, $CDCl_3$) δ 1.91(m, 6H), 2.72(m, 4H), 2.82(t, 2H), 3.61(m, 2H), 4.93(s, 2H), 5.69(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.89(d, 2H), 7.97(d, 2H), 8.12(s, 1H), 8.73(s, 1H)	503

TABLE 4-continued

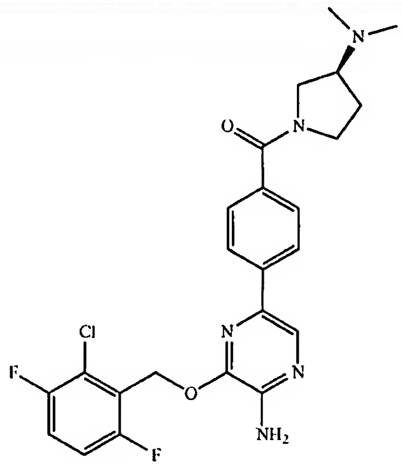
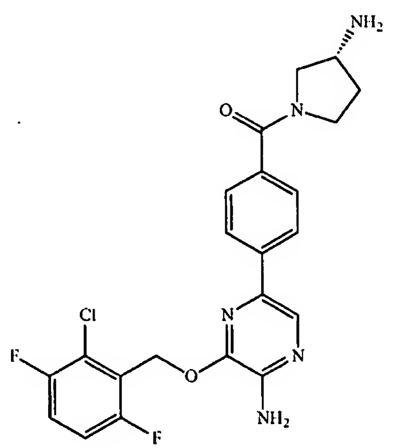
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-39		{4-[5-Amino-8-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.67	see examples	(300 MHz, $CDCl_3$) δ 1.70–2.10(m, 1H), 2.24(s, 3H), 2.34(s, 3H), 2.60–2.90(m, 1H), 3.30–4.00 (m, 4H), 4.90(s, 2H), 5.68(d, 2H), 7.10(m, 1H), 7.20(m, 1H), 7.60(m, 2H), 7.97(d, 2H), 8.13 (s, 1H)	489
II-40		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-dimethylamino-pyrrolidin-1-yl]-methanone	0.46	see examples	(300 MHz, CD_3OD) δ 1.80–2.40(m, 2H), 2.24(s, 3H), 3.30–3.90(m, 5H), 5.71(s, 2H), 7.25(m, 1H), 7.35(m, 1H), 7.60(m, 2H), 8.03(d, 2H), 8.10(s, 1H)	461

TABLE 4-continued

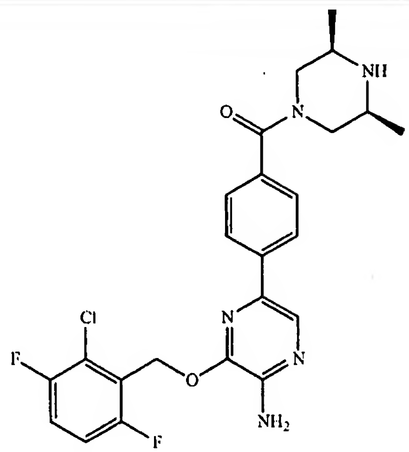
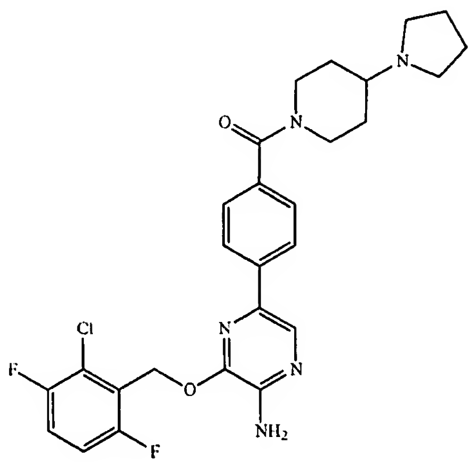
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-41		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	0.48	see examples	(300 MHz, $CDCl_3$) δ 0.9–1.2(m, 6H), 2.2–3.2(m, 6H), 4.91(s, 2H), 5.68(s, 2H), 7.10(m, 1H), 7.20 (m, 1H), 7.48(d, 2H), 7.97(d, 2H), 8.12(s, 1H)	489
II-42		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.33	see examples	(300 MHz, $CDCl_3$) δ 1.60–3.40(m, 17H), 4.89(s, 2H), 5.68(d, 2H), 7.10(m, 1H), 7.20(m, 1H), 7.47(d, 2H), 7.96(d, 2H), 8.11(s, 1H)	528

TABLE 4-continued

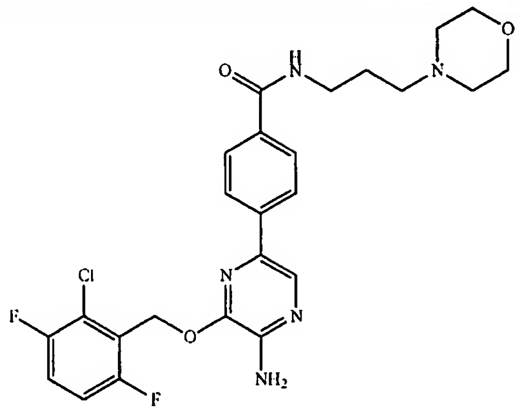
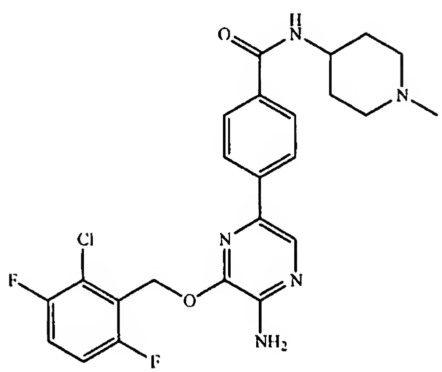
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-43		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	0.59	see examples	(300 MHz, $CDCl_3$) δ 1.83(m, 2H), 2.60(m, 6H), 3.61(m, 2H), 3.76(m, 4H), 4.93(s, 2H), 5.70(d, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.88(d, 2H), 8.00(d, 2H), 8.14(s, 1H)	518
II-44		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	0.5	see examples	(300 MHz, $CDCl_3$) δ 1.80(m, 2H), 2.07(m, 2H), 2.22(m, 2H), 2.34(s, 3H), 2.88(m, 2H), 4.04(m, 2H), 4.92(s, 2H), 5.69(d, 2H), 6.03(d, 1H), 7.05 (m, 1H), 7.20(m, 1H), 7.82(d, 2H), 7.98(d, 2H), 8.13(s, 1H)	489

TABLE 4-continued

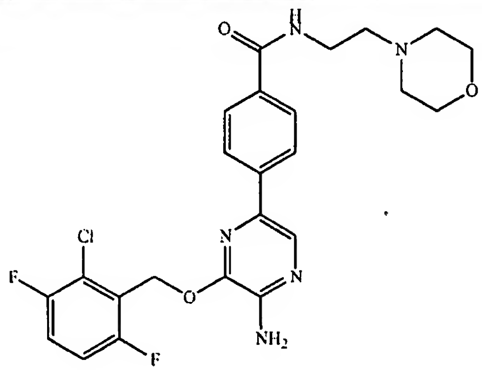
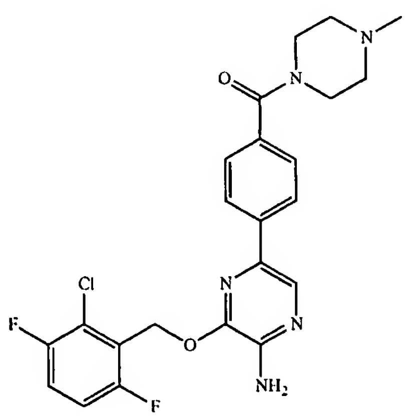
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-45		4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	1.11	see examples	(300 MHz, CD_3OD) δ 2.68(m, 6H), 3.60(m, 2H), 3.75(m, 4H), 5.72(s, 2H), 7.25(m, 1H), 7.35(m, 1H), 7.88(d, 2H), 8.05(d, 2H), 8.12(s, 1H)	504
II-46		{4-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.68	see examples	(300 MHz, $CDCl_3$) δ 2.39(s, 3H), 2.48(m, 4H), 3.69(m, 4H), 4.89(s, 2H), 5.69(s, 2H), 7.08(m, 1H), 7.20(m, 1H), 7.52(d, 2H), 7.95(d, 2H), 8.08 (s, 1H)	474

TABLE 4-continued

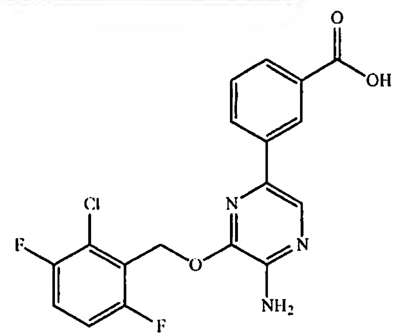
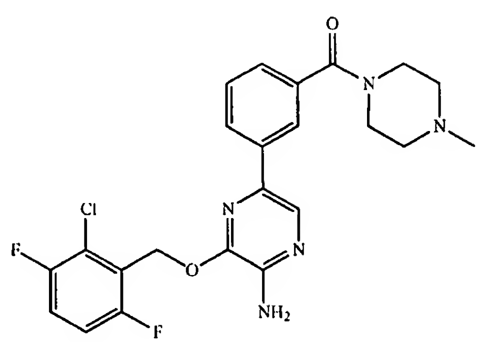
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-47		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzoic acid		see examples		392
II-48		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	2.85	see examples	(300 MHz, $CDCl_3$) δ 2.33(s, 3H), 2.46(m, 4H), 3.68(m, 4H), 4.86(br s, 2H), 5.67(s, 2H), 7.08 (m, 1H), 7.20(m, 1H), 7.35(d, 1H), 7.47(t, 1H), 7.95(m, 2H), 8.10(s, 1H)	474

TABLE 4-continued

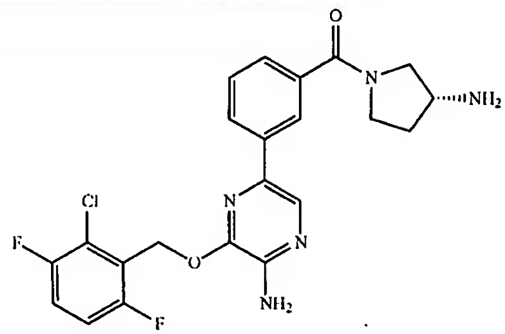
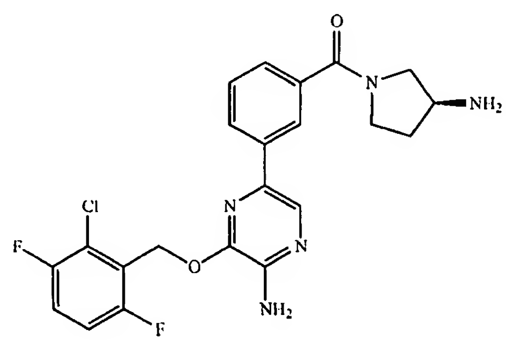
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-49		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3R)-3-amino-pyrrolidin-1-yl]-methanone	1.02	see examples	(300 MHz, CD_3OD) δ 2.12(m, 1H), 2.44(m, 1H), 3.52–4.05(m, 5H), 5.77(s, 2H), 7.24(m, 1H), 7.38(m, 1H), 7.54(m, 2H), 8.02(s, 1H), 8.12(m, 2H)	460
II-50		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-amino-pyrrolidin-1-yl]-methanone	0.91	see examples	(300 MHz, CD_3OD) δ 2.12(m, 1H), 2.44(m, 1H), 3.52–4.05(m, 5H), 5.77(s, 2H), 7.24(m, 1H), 7.38 (m, 1H), 7.54(m, 2H), 8.02(s, 1H), 8.12(m, 2H)	460

TABLE 4-continued

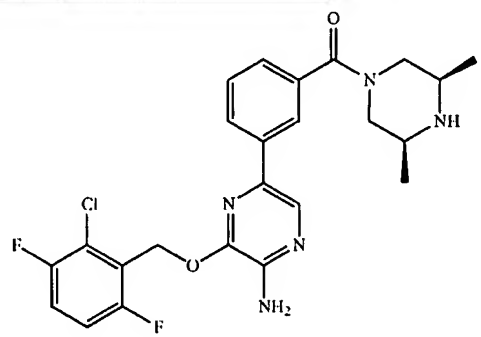
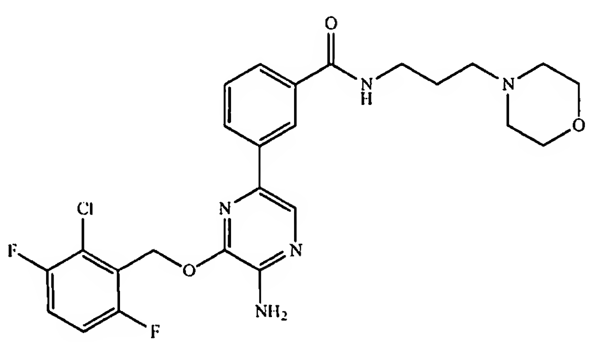
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-51		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone	2.56	see examples	(300 MHz, $CDCl_3$) δ 0.99(br d, 3H), 1.15(br d, 3H), 2.42(m, 1H), 2.70(m, 1H), 2.84(m, 1H), 2.93(m, 1H), 3.66(m, 1H), 4.67(m, 1H), 4.92(br s, 2H), 5.66(s, 2H), 7.05(m, 1H), 7.20(m, 1H), 7.35(m, 1H), 7.47(t, 1H), 7.97(m, 2H), 8.10(s, 1H)	488
II-52		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-morpholin-4-yl-propyl)-benzamide	4.2	see examples	(300 MHz, $CDCl_3$) δ 1.82(m, 2H), 2.50(m, 4H), 2.56(m, 2H), 3.67(m, 6H), 4.88(br s, 2H), 5.68 (s, 2H), 7.05(m, 1H), 7.19(m, 1H), 7.48(t, 1H), 7.70(d, 1H), 7.90(m, 1H), 8.06(d, 1H), 8.14(s, 1H), 8.38(t, J=1.6 Hz, 1H)	519

TABLE 4-continued

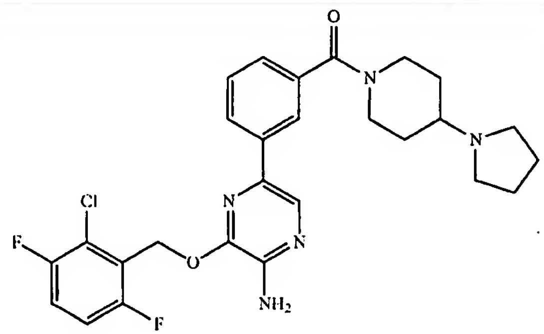
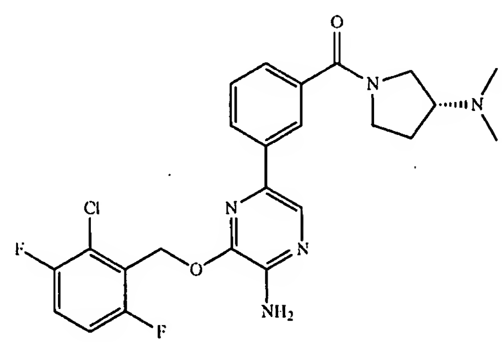
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-53		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.83	see examples	(300 MHz, $CDCl_3$) δ 1.60(m, 2H), 1.80(m, 4H), 1.88(m, 2H), 2.00(m, 2H), 2.32(m, 1H), 2.61 (m, 4H), 2.56(m, 2H), 3.00(m, 2H), 3.82(m, 1H), 4.66(m, 1H), 4.93(br s, 2H), 5.66(s, 2H), 7.06 (m, 1H), 7.18(m, 1H), 7.32(dt, 1H), 7.46(t, 1H), 7.70(d, 1H), 7.97(m, 2H), 8.09(d, J=3.6Hz, 1H)	528
II-54		{3-[5-Amino-6-(2-chloro-3.6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(3S)-3-dimethylamino-pyrrolidin-1-yl]-methanone	1.45	see examples	(300 MHz, $CDCl_3$) δ 1.85(m, 1H), 2.10(m, 1H),2.21 (s, 3H), 2.31(s, 3H), 2.75(m, 1H), 3.42(m, 1H), 3.64(m, 2H), 3.92(m, 1H), 4.93(br s, 2H), 5.67(s, 2H), 7.06(m, 1H), 7.18(m, 1H), 7.46(m, 2H), 7.97(m, 1H), 8.09(m, 2H)	488

TABLE 4-continued

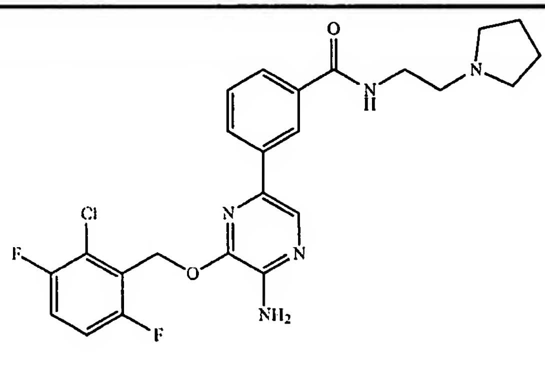
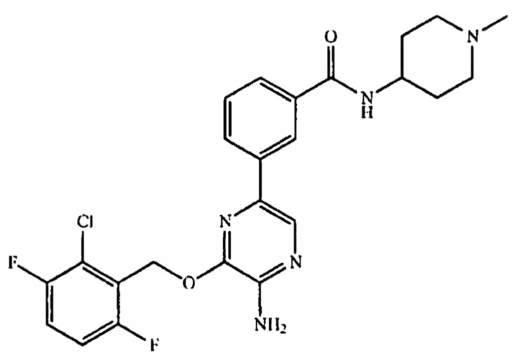
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-55		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	1.6	see examples	(300 MHz, $CDCl_3$) δ 1.82(m, 4H), 2.69(m, 4H), 2.84(m, 2H), 3.65(m, 2H), 4.93 (br s, 2H), 5.68 (s, 2H), 7.06(m, 1H), 7.18(m, 1H), 7.22(m, 1H), 7.49(t, J=7.7 Hz, 1H), 7.77(d, J=7.8 Hz, 1H), 8.04(dt, J=7.9 Hz, 1.5 Hz, 1H), 8.13(s, 1H), 8.38(t, J=1.5 Hz, 1H)	488
II-56		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	0.9	see examples	(300 MHz, $CDCl_3$) δ 1.71(m, 2H), 2.11(m, 2H), 2.28(t, 2H), 2.95(m, 2H), 4.11(m, 1H), 4.89(s, 2H), 5.69(s, 2H), 6.28(m, 1H), 7.08(m, 1H), 7.18 (m, 1H), 7.45(t, 1H), 7.68(d, 1H), 8.06(d, 1H), 8.11(s, 1H), 8.35(s, 1H)	488

TABLE 4-continued

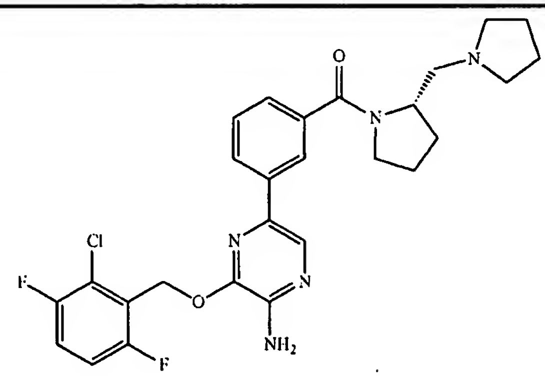
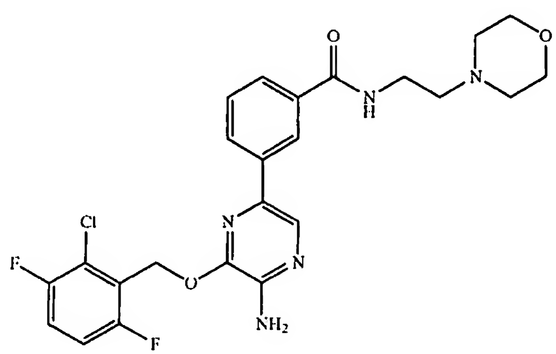
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-57		{3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-phenyl}-[(2S)-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl]-methanone	0.63	see examples	(300 MHz, $CDCl_3$) δ 2.02(m, 10H), 2.75(m, 4H), 3.49(m, 2H), 4.51(m, 1H), 4.89(s, 2H), 5.69(s, 2H), 7.08(m, 1H), 7.20(m, 1H), 7.48(m, 2H), 7.98(m, 1H), 8.07(m, 1H), 8.11(s, 1H)	528
II-58		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	2.5	see examples	(300 MHz, CD_3OD) δ 2.51(m, 4H), 2.65(t, 2H), 3.58(t, 2H), 3.69(m, 4H), 5.72(s, 2H), 7.20(m, 1H), 7.35(m, 1H), 7.52(t, 1H), 7.76(d, 1H), 8.12 (m, 2H), 8.41(s, 1H)	504

TABLE 4-continued

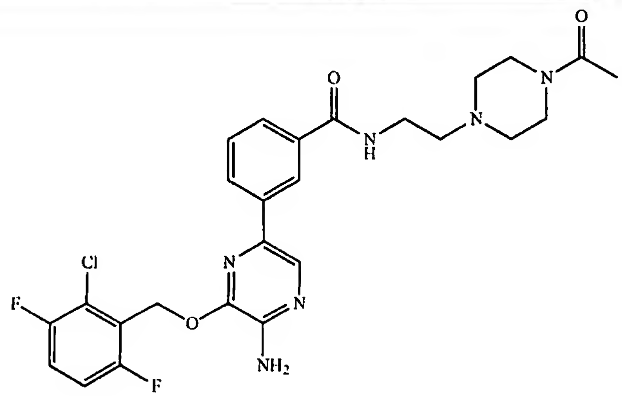
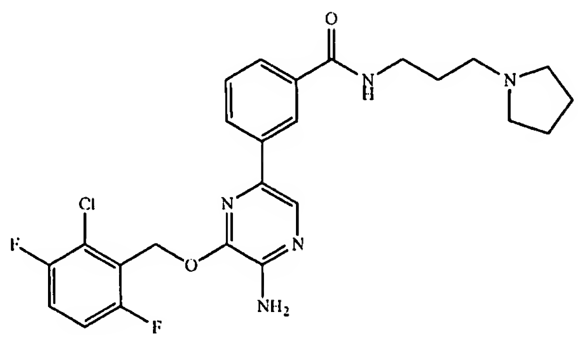
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-59		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-benzamide	2.77	see examples	(300 MHz, CD_3OD) δ 2.08(s, 3H), 2.59(m, 6H), 3.57(m, 6H), 5.71(s, 2H), 7.21(m, 1H), 7.37(m, 1H), 7.50(t, 1H), 7.75(d, 1H), 8.08(m, 2H), 8.39(s, 1H)	545
II-60		3-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-pyropyl)-benzamide	1.48	see examples	(300 MHz, $CDCl_3$) δ 1.79(m, 4H), 1.88(t, 2H), 2.65(m, 4H), 2.78(t, 2H), 3.65 (m, 2H), 4.86(s, 2H), 5.69(s, 2H), 7.06(m, 1H), 7.21(m, 1H), 7.45(t, 1H), 7.68(d, 1H), 8.06(d, 1H), 8.16(s, 1H), 8.40(s, 1H), 8.69(m, 1H)	502

TABLE 4-continued

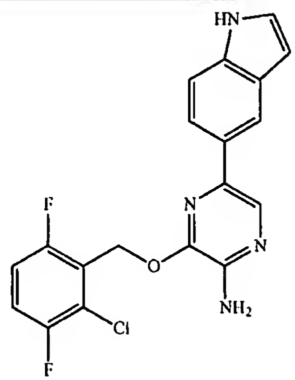
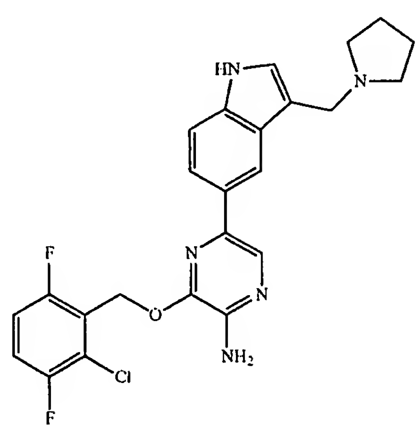
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-61		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(1H-indol-5-yl)-pyrazin-2-ylamine		see examples		387
II-62		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-pyrrolidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine	0.35	see examples	(300 MHz, $CDCl_3$) δ 1.78(m, 4H), 2.66(m, 4H), 3.89(s, 2H), 4.89(s, 2H), 5.69(s, 2H), 7.08(m, 1H), 7.18(m, 2H), 7.39(d, 1H), 7.79(d, 1H), 8.08 (s, 1H), 8.18(s, 1H), 8.79(s, 1H)	470

TABLE 4-continued

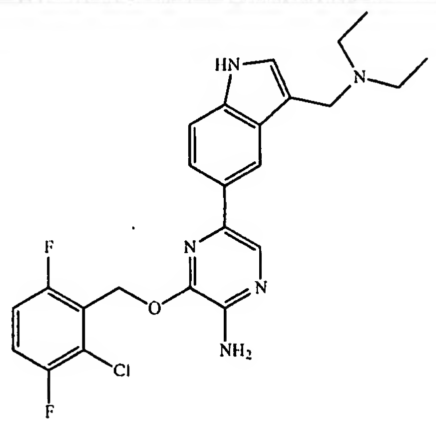
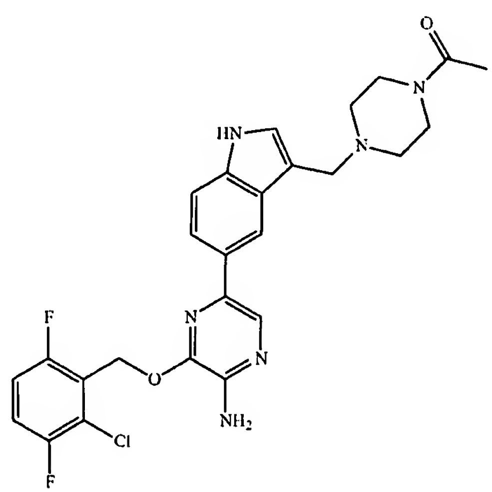
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-63		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-diethylaminomethyl-1H-indol-5-yl)-pyrazin-2-ylamine	0.73	see examples	(300 MHz, $CDCl_3$) δ 1.11(m, 6H), 2.69(m, 4H), 3.80(s, 2H), 4.69(s, 2H), 5.77(s, 2H), 7.02(m, 1H), 7.21(m, 2H), 7.45(d, 1H), 7.89(d, 1H), 8.22 (m, 3H)	472
II-64		1-(4-{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl}-piperazin-1-yl)-ethanone	1.5	see examples	(300 MHz, $CDCl_3$) δ 2.08(s, 3H), 2.55(m, 4H), 3.45(m, 2H), 3.64(m, 2H), 3.81(s, 2H), 4.78 (s, 2H), 5.71(s, 2H), 7.08(m, 1H), 7.18(m, 2H), 7.31 (d, 1H), 7.79(d, 1H), 8.04(s, 1H), 8.22(s, 1H), 8.49(s, 1H)	527

TABLE 4-continued

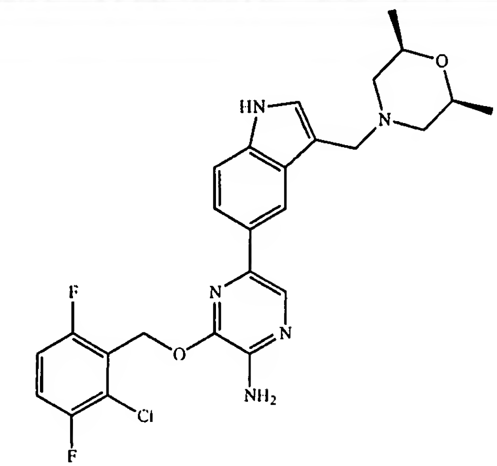
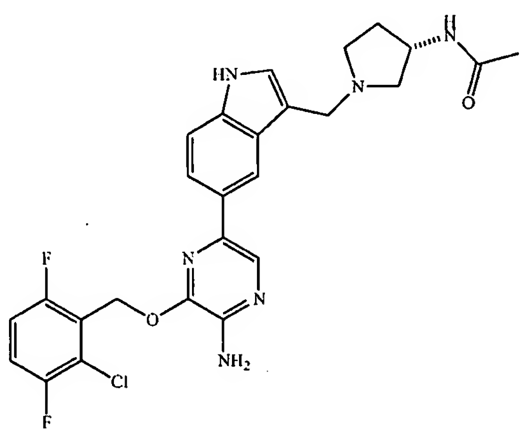
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-65		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-[3-(2,6-dimethyl-morpholin-4-ylmethyl)-1H-indol-5-yl]-pyrazin-2-ylamine	2.4	see examples	(300 MHz, $CDCl_3$) δ 1.11(d, 6H), 1.98(m, 2H), 2.98(m, 2H), 3.87(m, 4H), 4.75(s, 2H), 5.78(s, 2H), 7.08(m, 1H), 7.27(m, 2H), 7.48(d, 1H), 7.89(d, 1H), 8.19(s, 1H), 8.28(s, 2H)	514
II-66		N-(1-{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-1H-indol-3-ylmethyl}-(3S)-pyrrolidin-3-yl)-acetamide	0.55	see examples	(300 MHz, $CDCl_3$) δ 1.69(m, 1H), 1.88(s, 3H), 2.39(m, 2H), 2.75(m, 2H), 3.08(m, 1H), 3.95 (m, 2H), 4.50(m, 1H), 4.79(s, 2H), 5.78(s, 2H), 6.01 (m, 1H), 7.05(m, 1H), 7.18(m, 2H), 7.42(d, 1H), 7.79(d, 1H), 8.12(s, 1H), 8.21(s, 1H), 8.28(s, 1H)	527

TABLE 4-continued

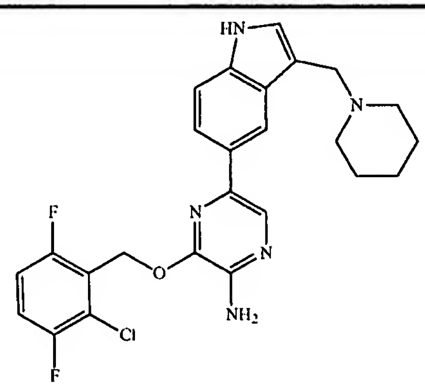
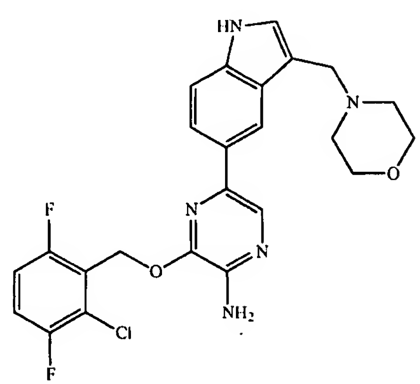
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-67		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-piperidin-1-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine	0.51	see examples	(300 MHz, $CDCl_3$) δ 1.49(m, 2H), 1.71(m, 4H), 2.66(m, 4H), 3.89(s, 2H), 4.79(s, 2H), 5.69 (s, 2H), 7.08(m, 1H), 7.18(m, 1H), 7.31(s, 1H), 7.42(d, 1H), 7.78(d, 1H), 8.08(s, 1H), 8.18(s, 1H), 8.69(br s, 1H)	484
II-68		3-(2-Chloro-3,6-difluoro-benzyloxy)-5-(3-morpholin-4-ylmethyl-1H-indol-5-yl)-pyrazin-2-ylamine	1.15	see examples	(300 MHz, $CDCl_3$) δ 2.72(m, 4H), 3.80(m, 6H), 4.73(s, 2H), 5.73(s, 2H), 7.06(m, 1H), 7.20(m, 1H), 7.46(d, 1H), 7.80(dd, 1H), 8.12(s, 1H), 8.25(s, 1H)	486

TABLE 4-continued

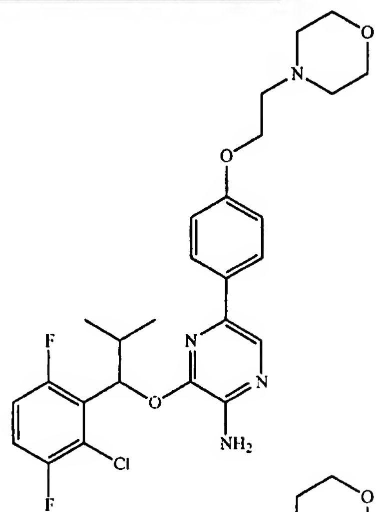
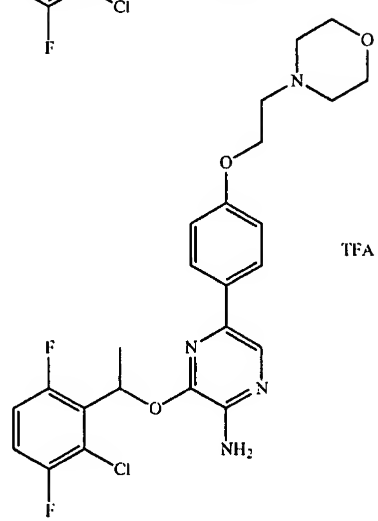
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-69		3-[1-(2-Chloro-3,6-difluoro-phenyl)-2-methyl-propoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine	10.58	see examples	(400 MHz, DMSO-d_6) δ 0.89(d, 3H), 1.19 (d, 3H), 2.47(m, 4H), 2.56(m, 1H), 2.68(t, 2H), 3.56 (t, 4H), 4.07(t, 2H), 5.96(d, 1H), 6.28(s, 2H), 6.89(d, 2H), 7.26(m, 1H), 7.38(m, 1H), 7.63(d, 2H), 7.95(s, 1H)	519
II-70		3-[1-(2-Chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; compound with trifluoro-acetic acid	0.51	see examples	(400 MHz, DMSO-d_6) δ 1.78(d, 3H), 3.21(m, 2H), 3.51(m, 2H), 3.54(m, 2H), 3.74(m, 2H), 3.98(m, 2H), 4.38(t, 2H), 6.34(br s, 2H), 6.42 (m, 1H), 6.97(d, 2H), 7.25(m, 1H), 7.38(m, 1H), 7.66(d, 2H), 7.86(s, 1H)	491

TABLE 4-continued

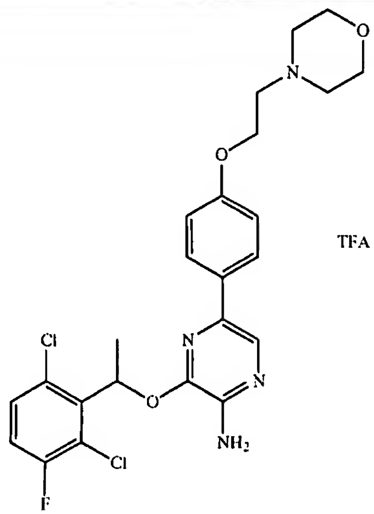
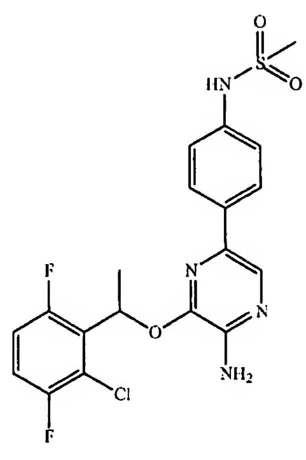
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-71		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrazin-2-ylamine; compound with trifluoro-acetic acid	0.3	see examples	(400 MHz, DMSO-d_6) δ 1.79(d, 3H), 3.21(m, 2H), 3.46(m, 2H), 3.57(m, 2H), 3.74(m, 2H), 3.95(m, 2H), 4.36(t, 2H), 6.34(br s, 2H), 6.49 (m, 1H), 6.94(d, 2H), 7.37(t, 1H), 7.48(m, 1H), 7.66(d, 2H), 7.98(s, 1H)	491
II-72		N-(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-methanesulfonamide		see examples	(400 MHz, DMSO-d_6) δ 1.78(d, 3H), 2.96(s, 3H), 6.41(m, 3H), 7.15(d, 2H), 7.26(m, 1H), 7.37(m, 1H), 7.64(d, 2H), 8.00(s, 1H), 9.72(s, 1H)	455

TABLE 4-continued

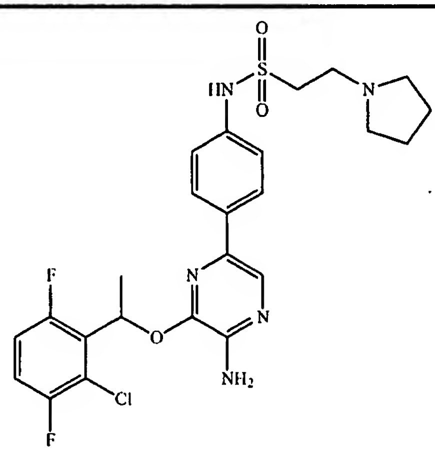
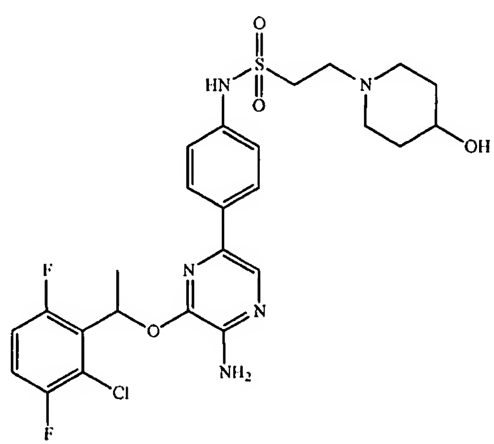
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-73		2-Pyrrolidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.84(m, 7H), 2.56(m, 4H), 3.04(m, 2H), 3.25(m, 2H), 4.94(br s, 2H), 6.71 (q, 1H), 6.95(m, 2H), 7.21(d, 2H), 7.72(d, 2H), 7.96(s, 1H)	538
II-74		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.60(m, 2H), 1.82(m, 5H), 2.23(m, 2H), 2.77(m, 2H), 2.89(t, 2H), 3.26(t, 2H), 3.74(m, 1H), 5.07(br s, 2H), 6.70(q, 1H), 7.00(m, 2H), 7.24(d, 2H), 7.73(d, 2H), 7.94 (s, 1H)	568

TABLE 4-continued

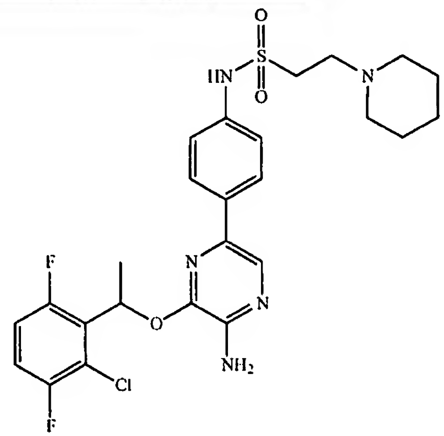
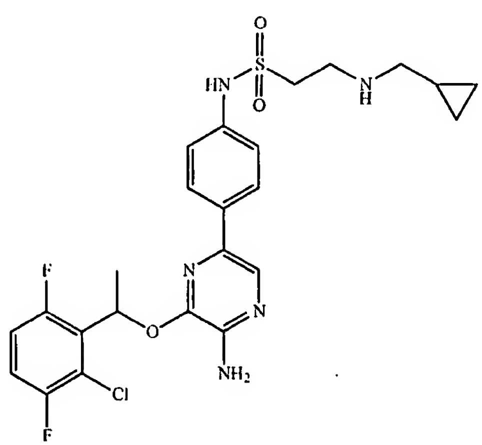
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-75		2-Piperidin-1-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.49(m, 2H), 1.61(m, 4H), 1.83(d, 3H), 2.50(m, 4H), 2.86(m, 2H), 3.20(m, 2H), 4.95(br s, 2H), 6.70(q, 1H), 7.00(m, 2H), 7.24(d, 2H), 7.74(d, 2H), 7.96(s, 1H)	552
II-76		2-(Cyclopropylmethyl-amino)-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 0.14(m, 2H), 0.50(m, 2H), 0.95(m, 1H), 1.82(d, 3H), 2.49(m, 2H), 3.20(m, 4H), 4.73(br s, 1H), 5.02(br s, 2H), 6.71(q, 1H), 7.00(m, 2H), 7.25(d, 2H), 7.74(d, 2H), 7.96(s, 1H)	538

TABLE 4-continued

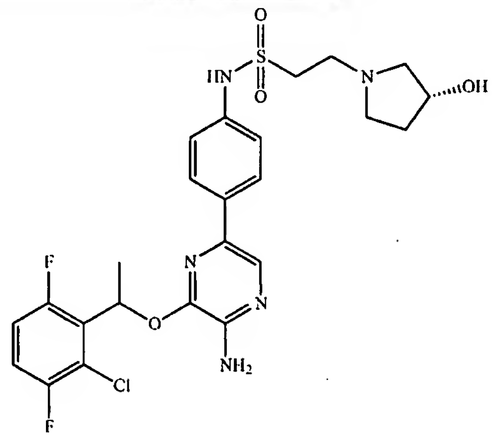
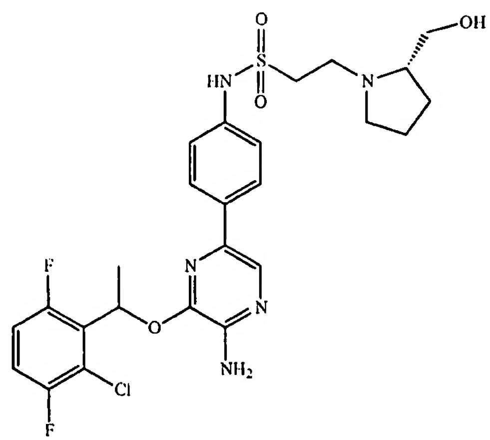
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-77		2-[(3R)-3-Hydroxy-pyrrolidin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.79(m, 1H), 1.82(d, 3H), 2.26(m, 2H), 2.54(m, 1H), 2.82(m, 1H), 2.98 (m, 2H), 3.08(m, 1H), 3.26(m, 2H), 4.44(m, 1H), 4.94(br s, 1H), 6.70(q, 1H), 7.00(m, 2H), 7.29(d, 2H), 7.73(d, 2H), 7.96(s, 1H)	554
II-78		2-[(2S)-2-Hydroxymethyl-pyrrolidin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.79(m, 4H), 1.82(d, 3H), 2.15(m, 1H), 2.66(m, 2H), 2.98(m, 2H), 3.35 (m, 1H), 3.48(m, 1H), 3.54(m, 1H), 3.92(m, 1H), 4.97(br s, 1H), 6.70(q, 1H), 7.00(m, 2H), 7.28(d, 2H), 7.71(d, 2H), 7.95(s, 1H)	568

TABLE 4-continued

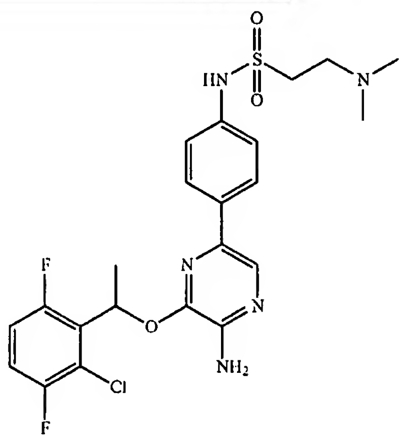
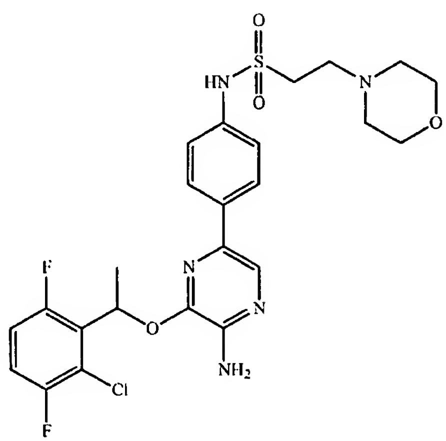
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-79		2-Dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.82(d, 3H), 2.29(s, 6H), 2.85(t, 2H), 3.21(t, 2H), 5.00(br s, 2H), 6.71(q, 1H), 7.00(m, 2H), 7.23(d, 2H), 7.74(d, 2H), 7.96 (s, 1H)	512
II-80		2-Morpholin-4-yl-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.82(d, 3H), 2.48(m, 4H), 2.90(m, 2H), 3.27(m, 2H), 3.71(m, 4H), 4.92(br s, 2H), 6.71(q, 1H), 7.00(m, 2H), 7.24(d, 2H), 7.74(d, 2H), 7.97(s, 1H)	554

TABLE 4-continued

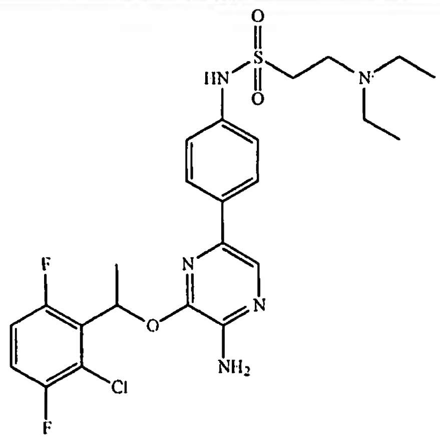
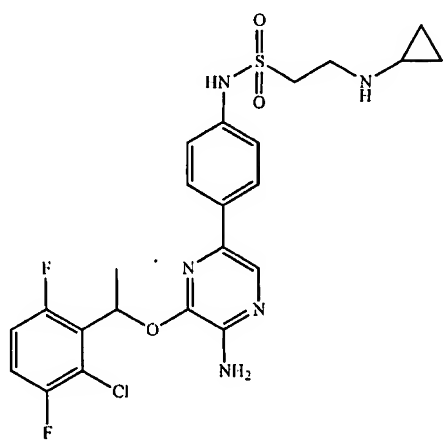
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-81		2-Diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 1.07(t, 6H), 1.82(d, 3H), 2.60(q, 4H), 3.02(t, 2H), 3.22(t, 2H), 4.95(br s, 2H), 6.71(q, 1H), 7.00(m, 2H), 7.22(d, 2H), 7.74 (d, 2H), 7.96(s, 1H)	540
II-82		2-Cyclopropylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl]-phenyl)-amide		see examples	(300 MHz, $CDCl_3$) δ 0.38(m, 2H), 0.50(m, 2H), 1.82(d, 3H), 2.15(m, 1H), 3.24(m, 4H), 4.93(br s, 2H), 6.71(q, 1H), 7.00(m, 2H), 7.21(d, 2H), 7.74(d, 2H), 7.97(s, 1H)	540

TABLE 4-continued

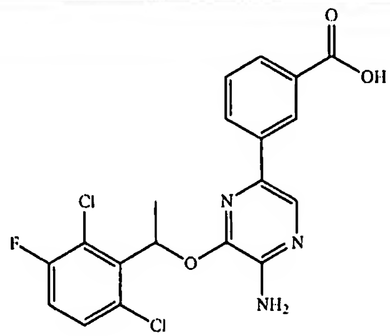
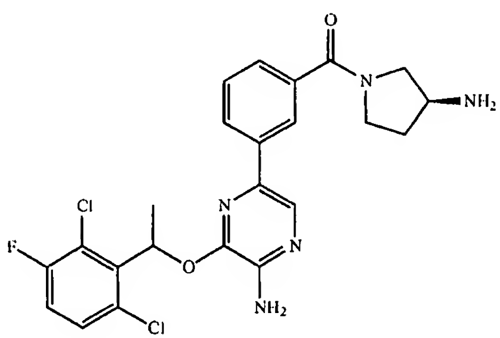
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-83		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid	1.36	see examples		423
II-84		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3S)-3-amino-pyrrolidin-1-yl)-m-ethanone	0.069	see examples	(300 MHz, MeOD) δ 7.84(d, 1H), 7.71(m, 2H), 7.38(m, 3H), 7.10(m, 1H), 6.60(m, 1H), 4.86(s, 2H), 4.20(m, 1H), 3.45–3.89(m, 4H), 1.82(d, 3H), 1.34(m, 1H), 0.89(m, 1H)	492

TABLE 4-continued

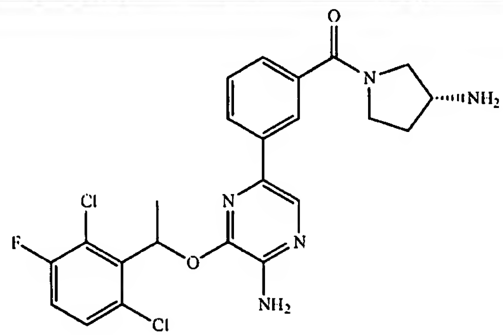
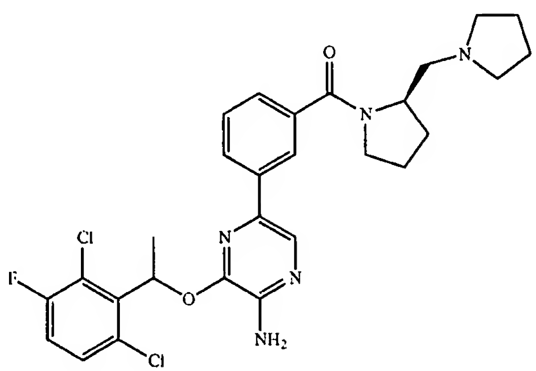
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-85		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(3R)-3-amino-pyrrolidin-1-yl)-m-ethanone	0.11	see examples	(300 MHz, McOD) δ 7.84(d, 1H), 7.71(m, 2H), 7.38(m, 3H), 7.10(m, 1H), 6.60(m, 1H), 4.86(s, 2H), 4.20(t, 1H), 3.45–3.89(m, 4H), 1.82(d, 3H), 1.34(m, 1H), 0.89(m, 1H)	492
II-86		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(2R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.15	see examples	(300 MHz, $CDCl_3$) δ 8.04(d, 1H), 7.84(d, 2H), 7.30(d, 2H), 7.15(tert, 1H), 6.99(t, 1H), 5.89(m, 1H), 4.89(s, 2H), 4.44(s, 1H), 3.89(m, 1H), 3.65 (m, 1H), 3.30(m, 2H), 2.85(m, 3H), 1.82(d, 3H), 0.89–2.20(m, 9H)	558

TABLE 4-continued

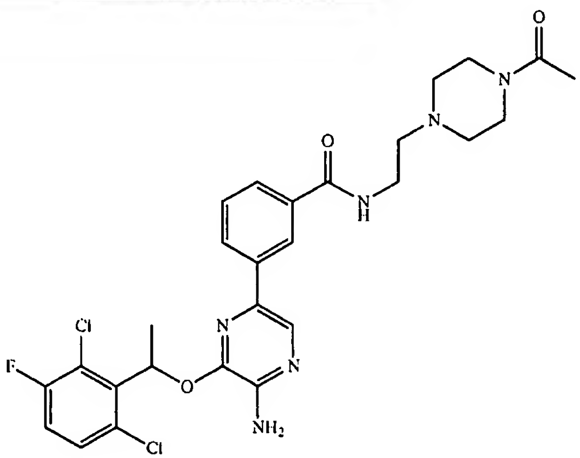
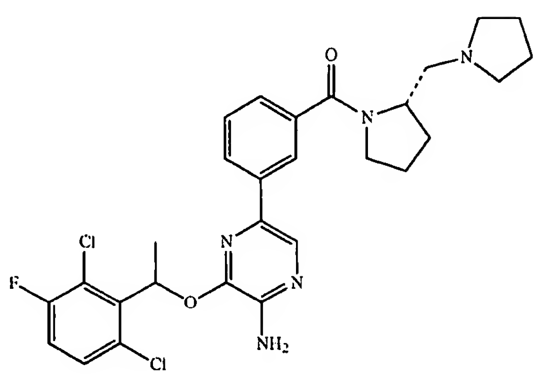
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-87		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide	0.186	see examples	(300 MHz, $CDCl_3$) δ 8.04(d, 1H), 7.99(s, 1H), 7.78(d, 1H), 7.60(d, 1H), 7.34(m, 2H), 7.15(t, 1H), 6.72(tert, 1H), 4.89(s, 2H), 4.56(m, 6H), 3.21(d, 3H), 2.60(t, 1H), 2.55(dd, 1H), 2.09(s, 3H), 1.80(d, 4H)	575
II-88		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-[(2S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.17	see examples	(300 MHz, MeOD) δ 8.04(d, 1H), 7.84(d, 2H), 7.35(m, 3H), 7.20(m, 1H), 6.60(m, 1H), 4.89(s, 2H), 4.44(s, 1H), 3.59(m, 1H), 3.30(m, 1H), 3.25(s, 2H), 3.16(m, 3H), 1.82(d, 3H), 0.89–2.32(m, 9H)	559

TABLE 4-continued

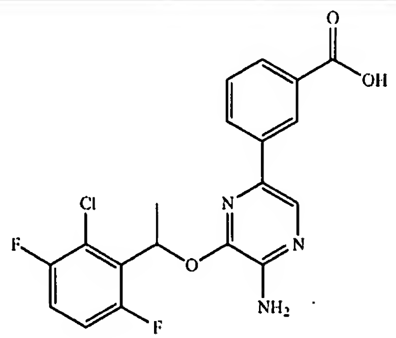
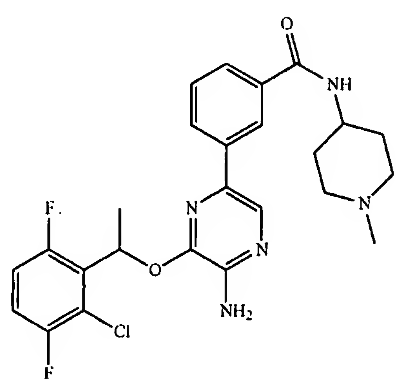
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-89		3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid	-	see examples		406
II-90		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.21	see examples	(300 MHz, $CDCl_3$) δ 8.20(s, 1H), 8.08(s, 1H), 7.89(d, 1H), 7.75(d, 1H), 7.44(t, 1H), 7.01(m, 2H), 6.78(m, 1H), 6.20(s, 1H), 4.98(s, 2H), 4.09 (m, 1H), 2.97(m, 2H), 2.39(s, 3H), 2.29(t, 2H), 2.12(m, 2H), 1.90(d, 3H), 1.79(m, 2H)	502

TABLE 4-continued

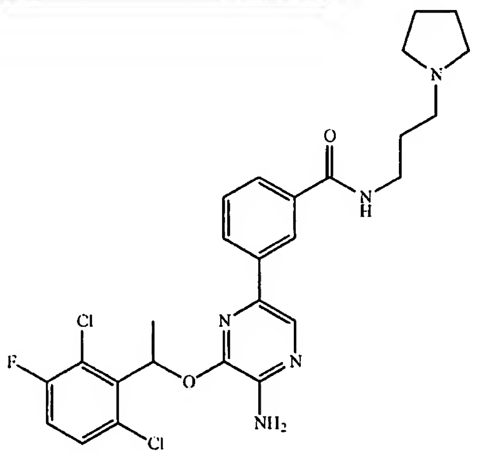
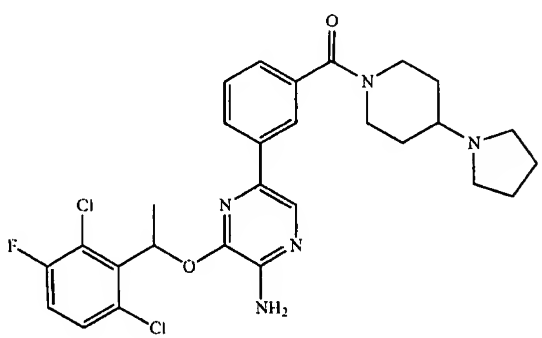
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-91		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.15	see examples	(300 MHz, CD_3OD) δ 8.15(s, 1H), 7.98(s, 1H), 7.80(d, 1H), 7.61(d, 1H), 7.35(m, 2H), 7.09(t, 1H), 6.69(m, 1H), 3.44(t, 2H), 2.55(m, 6H), 1.88 (d, 3H), 1.80(m, 6H)	532
II-92		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.15	see examples	(300 MHz, CD_3OD) δ 7.96(s, 1H), 7.76 (d, 1H), 7.65(m, 1H), 7.41(m, 2H), 7.21(d, 1H), 7.12(t, 1H), 6.61(m, 1H), 4.68(m, 2H), 3.62(m, 1H), 3.05(m, 2H), 2.69(m, 6H), 2.45(m, 2H), 2.12 (m, 2H), 1.86(d, 3H), 1.48(m, 2H)	558

TABLE 4-continued

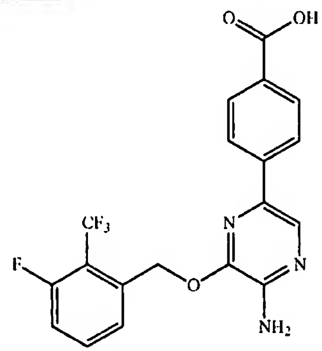
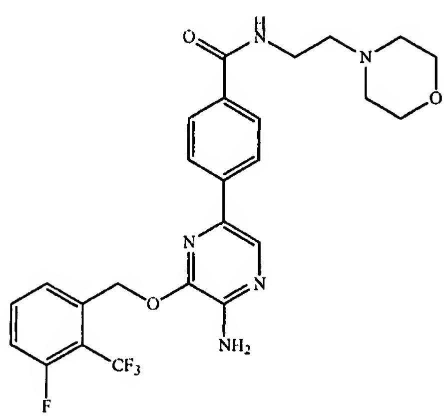
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-93		4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid		see examples		408
II-94		4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide	0.22	see examples	(300 MHz, $CDCl_3$) δ 8.14(s, 1H), 7.92(d, 2H), 7.84(d, 2H), 7.50(m, 1H), 7.42(m, 1H), 7.20(m, 1H), 6.75(s, 1H), 5.70(s, 2H), 4.97(s, 2H), 3.74 (m, 4H), 3.58(m, 2H), 2.62(m, 2H), 2.52(s, 4H)	520

TABLE 4-continued

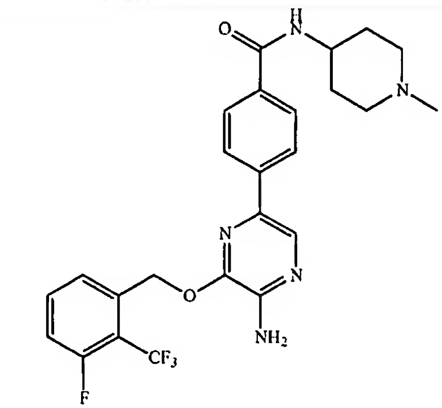
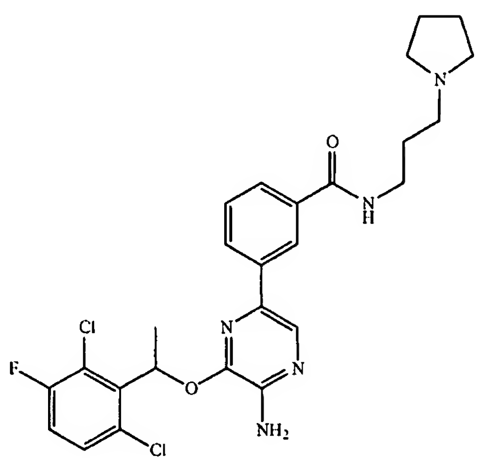
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-95		4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(1-methyl-piperidin-4-yl)-benzamide	0.081	see examples	(300 MHz, $CDCl_3$) δ 8.14(s, 1H), 7.92(d, 2H), 7.84(d, 2H), 7.50(m, 1H), 7.42(m, 1H), 7.20(m, 1H), 6.04(d, 1H), 5.75(s, 2H), 5.01(s, 2H), 4.0 (m, 1H), 2.85(d, 2H), 2.30(s, 3H), 2.20(t, 2H), 2.12(d, 2H), 1.59(m, 2H)	504
II-96		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.15	4 as in Example II-84	(300 MHZ, CD3OD) δ 8.18(s, 1H), 7.98(s, 1H), 7.80(d, 1H), 7.61(d, 1H), 7.35(m, 2H), 7.12(t, 1H), 6.75(q, 1H), 3.44(t, 2H), 2.55(m, 6H), 1.88(d, 3H), 1.80(m, 6H).	532

TABLE 4-continued

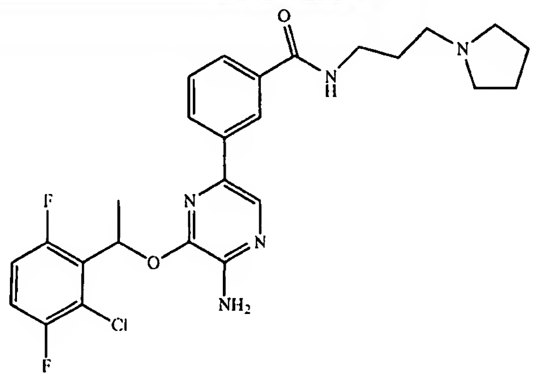
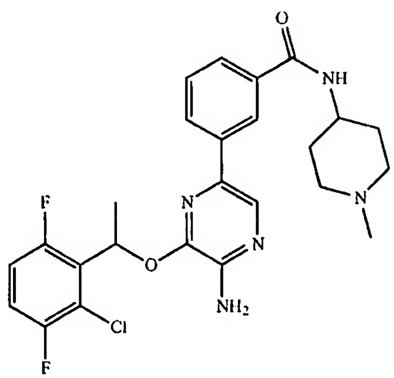
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-97		3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.35	4 as in Example II-90	(300 MHZ, CDCl3) δ 8.38(s, 1H), 8.18(s, 2H), 7.92(m, 2H), 7.48(t, 1H), 7.02(m, 2H), 6.78(q, 1H), 4.96(s, 2H), 3.72(m, 2H), 3.18(m, 2H), 2.83(m, 2H), 2.22(m, 2H), 2.08(m, 4H), 1.83 (d, 3H), 1.70(m, 2H).	516
II-98		3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.21	4 as in Example II-90	(300 MHZ, CDCl3) δ 8.20(s, 1H), 8.08(s, 1H), 7.89(d, 1H), 7.75(d, 1H), 7.44(t, 1H), 7.01(m, 2H), 6.78(q, 1H), 6.20 (bd, 1H), 4.98(s, 2H), 4.09(m, 1H), 2.97(m, 2H), 2.39(s, 3H), 2.29 (m, 2H), 2.12(m, 2H), 1.90(d, 3H), 1.79(m, 2H).	502

TABLE 4-continued

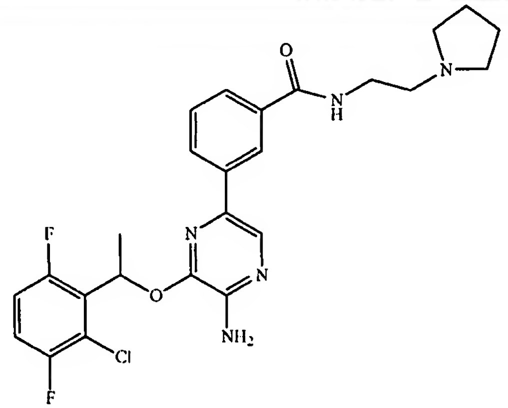
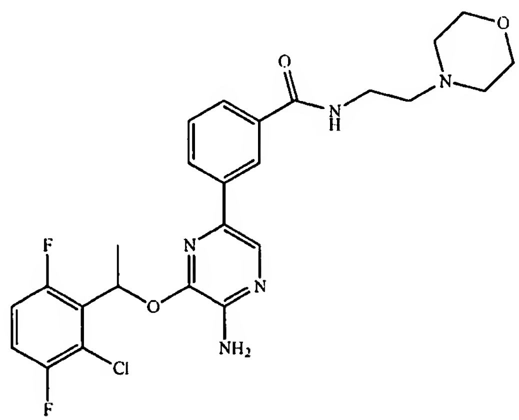
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-99		3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.18	4 as in Example II-90	(300 MHZ, CDCl3) δ 8.19(s, 1H), 8.09(s, 1H), 7.88(d, 1H), 7.78(d, 1H), 7.48 (t, 1H), 7.06 (bm, 1H), 6.96(m, 2H), 6.75(q, 1H), 5.08(s, 2H), 3.68(m, 2H), 2.88(m, 2H), 2.68(m, 4H), 1.86(m, 7H).	502
II-100		3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.31	4 as in Example II-90	(300 MHZ, CDCl3) δ 8.17(s, 1H), 8.08(s, 1H), 7.88(d, 1H), 7.68(d, 1H), 7.48 (t, 1H), 6.98(m, 2H), 6.80 (bt, 1H), 6.74(q, 1H), 5.02(s, 2H), 3.76(m, 4H), 3.68(m, 2H), 2.68(m, 2H), 2.58 (m, 4H), 1.85(d, 3H).	518

TABLE 4-continued

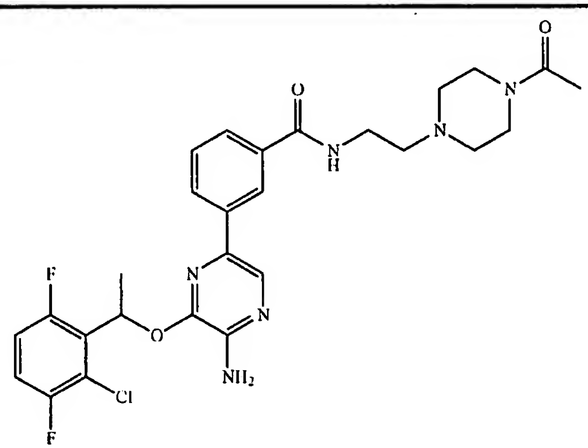
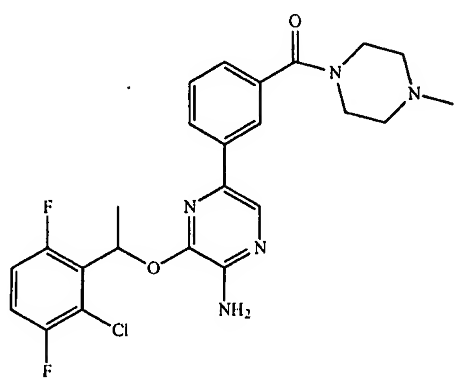
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-101		N-[2-(4-Acetyl-piperazin-1-yl) ethyl]-3-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide	0.64	4 as in Example II-90	(300 MHZ, CDCl3) δ 8.16(s, 1H), 8.03(s, 1H), 7.86(d, 1H), 7.68(d, 1H), 7.40(t, 1H), 6.98(m, 3H), 6.71(q, 1H), 5.13(s, 2H), 3.69(m, 4H), 3.51(m, 2H), 2.80(m, 2H), 2.66(m, 4H), 2.08 (s, 3H), 1.83(d, 3H).	559
II-102		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.82 (m, 2H), 7.41(t, 1H), 7.28(m, 1H), 6.95(m, 2H), 6.71(q, 1H), 5.00(s, 2H), 3.85(m, 2H), 3.46(m, 2H), 2.36(m, 4H), 2.33(s, 3H), 1.83(d, 3H).	488

TABLE 4-continued

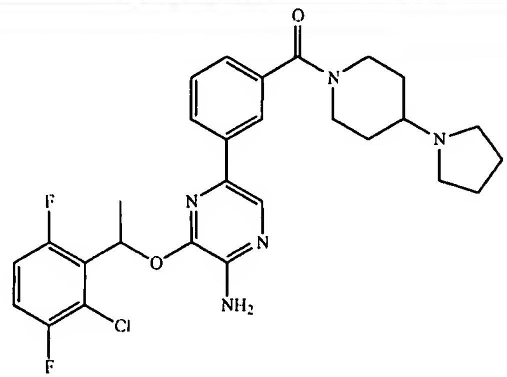
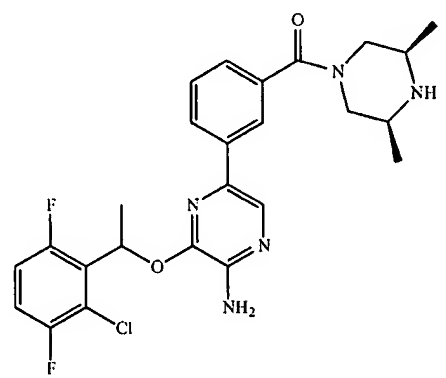
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-103		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.80(m, 2H), 7.41(t, 1H), 7.29(m, 1H), 6.95(m, 2H), 6.69(q, 1H), 4.97(s, 2H), 4.72(m, 1H), 3.83(m, 1H), 2.81(m, 7H), 1.83(d, 3H), 2.10–1.70(m, 8H).	542
II-104		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.03(s, 1H), 7.80(m, 2H), 7.41(t, 1H), 7.29(m, 1H), 6.95(m, 2H), 6.70(q, 1H), 5.00(s, 2H), 4.68 (m, 1H), 3.56(m, 1H), 2.75(m, 3H), 2.42(m, 1H), 1.83(d, 3H), 1.57(m, 1H), 1.15(m, 3H), 0.96(m, 3H).	502

TABLE 4-continued

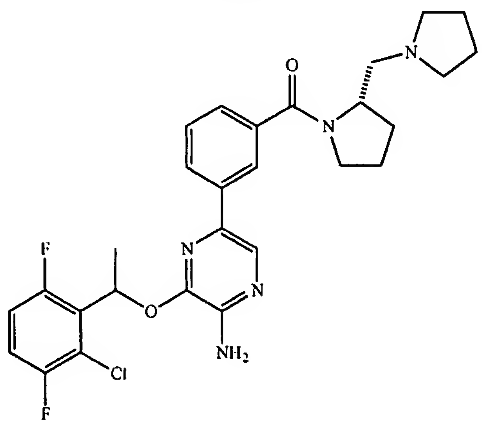
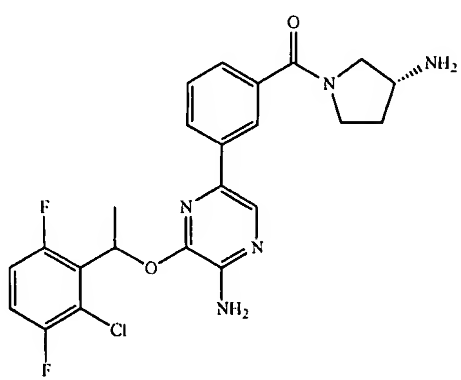
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-105		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.04(s, 1H), 7.83 (m, 2H), 7.39(m, 2H), 6.98(m, 2H), 6.70(q, 1H), 5.00 (s, 2H), 4.47(m, 1H), 3.50(m, 2H), 3.00(m, 5H), 2.30(m, 3H), 2.00(m, 5H), 1.83(d, 3H), 1.53(m, 1H).	542
II-106		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.83 (m, 2H), 7.40(m, 2H), 6.98(m, 2H), 6.70(q, 1H), 4.98 (s, 2H), 3.75(m, 4H), 3.61–3.15(m, 1H), 2.15 (m, 1H), 1.85(d, 3H), 1.95–1.75(m, 3H).	300

TABLE 4-continued

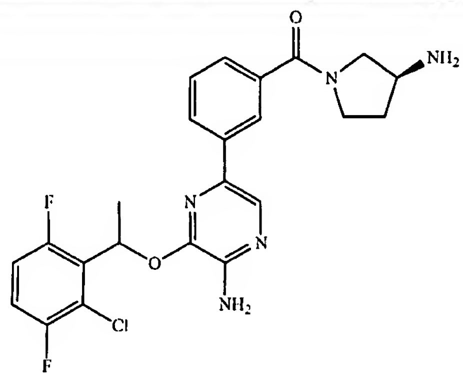
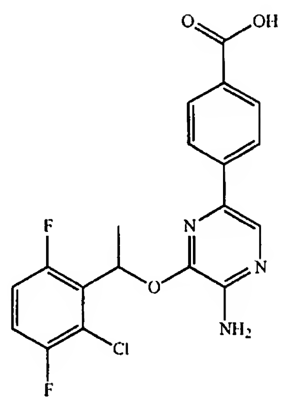
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-107		(3-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone		4 as in Example II-90	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.83(m, 2H), 7.40(m, 2H), 6.98(m, 2H), 6.70(q, 1H), 4.98 (s, 2H), 3.75(m, 4H), 3.61–3.15(m, 1H), 2.15 (m, 1H), 1.85(d, 3H), 1.95–1.75(m, 3H).	300
II-108		4-{-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid		3 as in Example I-211		406

TABLE 4-continued

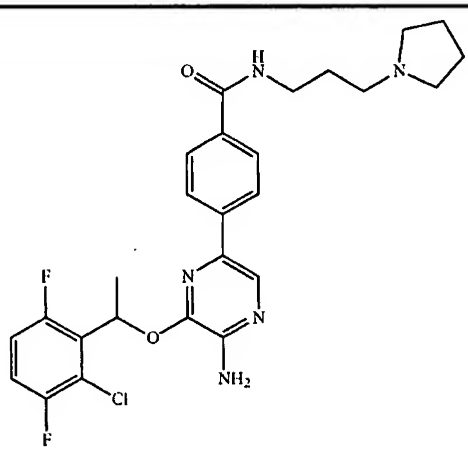
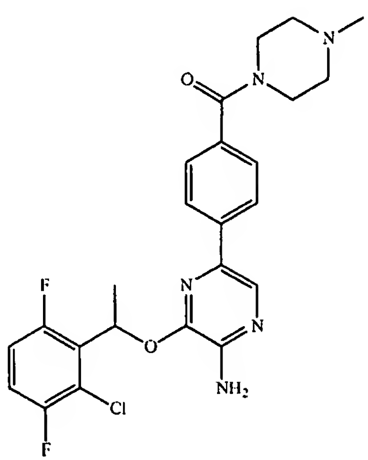
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-109		4-{-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.1	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.28 (bm, 1H), 8.04(m, 3H), 7.84(d, 2H), 6.95(m, 2H), 6.71(q, 1H), 5.03(s, 2H), 3.85(m, 2H), 3.72(m, 2H), 3.18 (m, 2H), 2.82(m, 2H), 2.25(m, 4H), 2.08(m, 2H), 1.87(d, 3H).	516
II-110		(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.16	4 as in Example II-109	(300 MHZ, CDCl3) δ 7.99(s, 1H), 7.78(d, 2H), 7.43(d, 2H), 7.29(m, 1H), 6.85(t, 1H), 6.94(q, 1H), 5.07(s, 2H), 3.75(m, 2H), 3.50(m, 2H), 2.43(m, 4H), 2.33(s, 3H), 1.84(d, 3H).	488

TABLE 4-continued

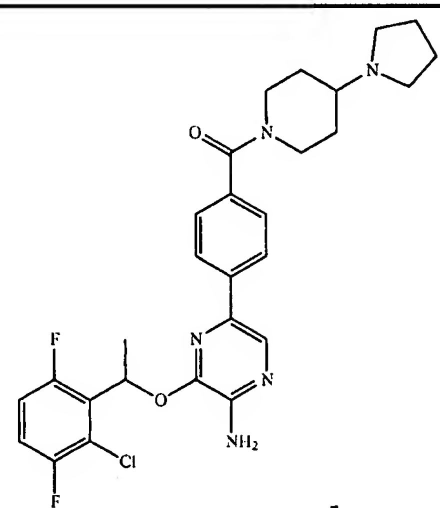
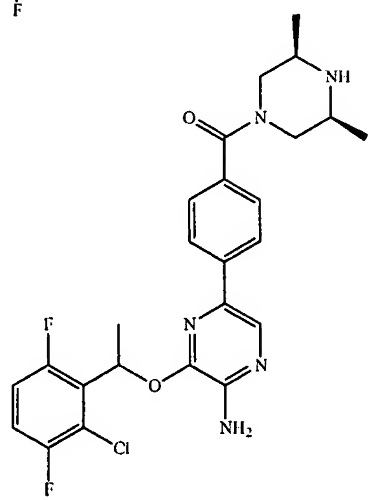
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-111		(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.17	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.81(d, 2H), 7.40(d, 2H), 6.99(m, 2H), 6.71(q, 1H), 5.02(s, 2H), 4.64(m, 1H), 3.85(m, 1H), 2.99(m, 2H), 2.67(m, 4H), 2.38(m, 1H), 1.90(m, 9H), 1.62(m, 2H).	542
II-112		4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.19	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.81(d, 2H), 7.38(d, 2H), 6.99(m, 2H), 6.71(q, 1H), 4.99(s, 2H), 4.65(m, 1H), 3.65(m, 1H), 2.88(m, 2H), 2.68(m, 1H), 2.41(m, 1H), 1.84(d, 3H), 1.64 (m, 1H), 1.18(s, 3H), 1.06(s, 3H).	502

TABLE 4-continued

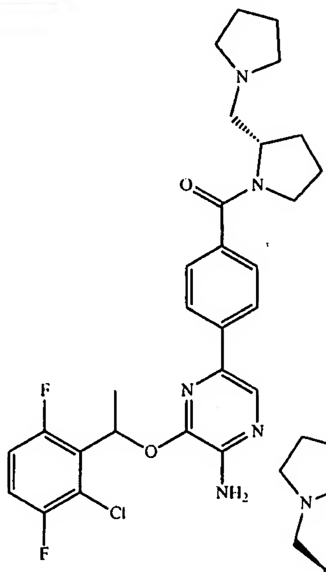
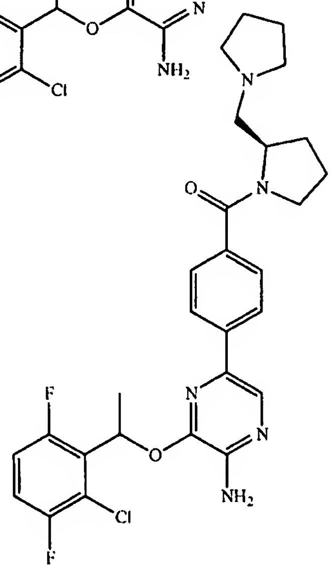
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-113		(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.18	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.07(s, 1H), 7.81(d, 2H), 7.53(d, 2H), 6.95(m, 2H), 6.69(q, 1H), 4.99(s, 2H), 4.45(m, 1H), 3.55(m, 2H), 2.95(m, 4H), 1.90–2.3(m, 9H), 1.82(d, 3H), 1.65(m, 1H).	542
II-114		(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.13	4 as in Example II-109	(300 MHZ, $CDCl_3$) δ 8.02(s, 1H), 7.81(d, 2H), 7.53(d, 2H), 6.95(m, 2H), 6.69(q, 1H), 4.99(s, 2H), 4.45(m, 1H), 3.55(m, 2H), 2.95(m, 4H), 2.21(m, 3H), 1.92(m, 6H), 1.82(d, 3H), 1.59(m, 1H).	542

TABLE 4-continued

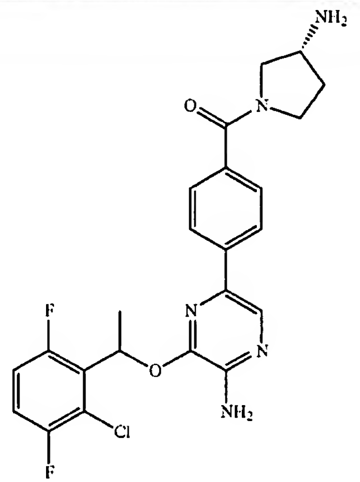
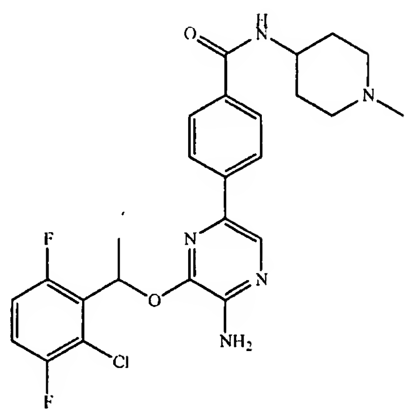
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-115		(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone	0.078	4 as in Example II-109	(300 MHZ, CD3OD) δ 8.02(s, 1H), 7.81(d, 2H), 7.53(d, 2H), 7.01(m, 2H), 6.69(q, 1H), 4.91(s, 2H), 3.85(m, 1H), 3.71(m, 2H), 3.55(m, 1H), 2.18(m, 1H), 1.85(d, 3H), 1.75(m, 1H), 1.42(m, 3H).	574
II-116		4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.19	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.06(s, 1H), 7.82(m, 4H), 7.00(m, 2H), 6.72(m, 2H), 5.04(s, 2H), 4.09 (m, 1H), 2.97(m, 2H), 2.39(s, 3H), 2.29(m, 2H), 2.12(m, 2H), 1.90(d, 3H), 1.79(m, 2H).	502

TABLE 4-continued

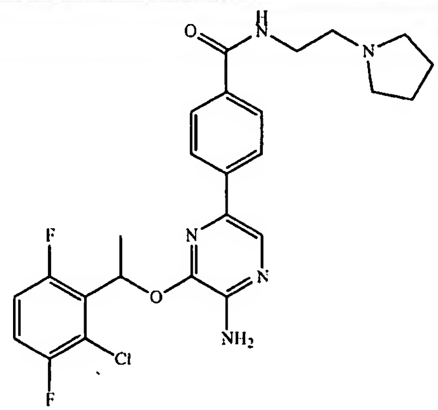
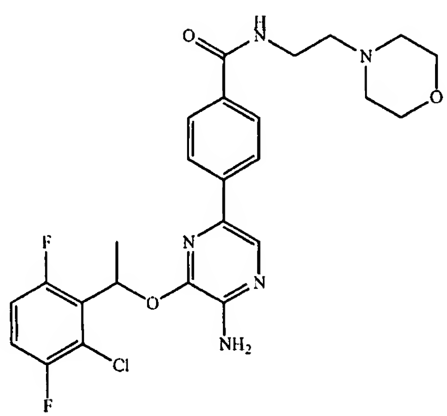
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-117		4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.11	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.06(s, 1H), 7.82(m, 4H), 7.00(m, 2H), 6.72(m, 2H), 5.04(s, 2H), 3.68 (m, 2H), 2.88(m, 2H), 2.68(m, 4H), 1.86(m, 7H).	502
II-118		4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.26	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.06(s, 1H), 7.82(m, 4H), 7.00(m, 2H), 6.72(m, 2H), 5.04(s, 2H), 3.75 (m, 4H), 3.56(m, 2H), 2.62(t, 2H), 2.52(m, 4H), 1.83(d, 3H).	518

TABLE 4-continued

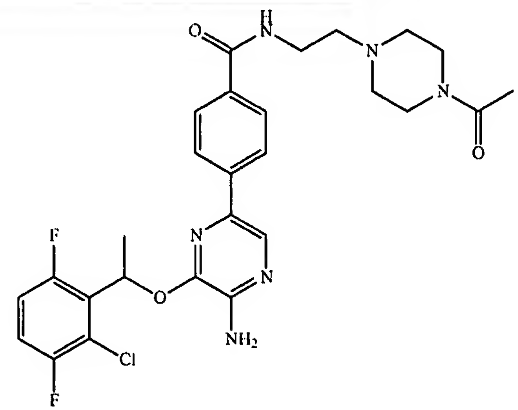
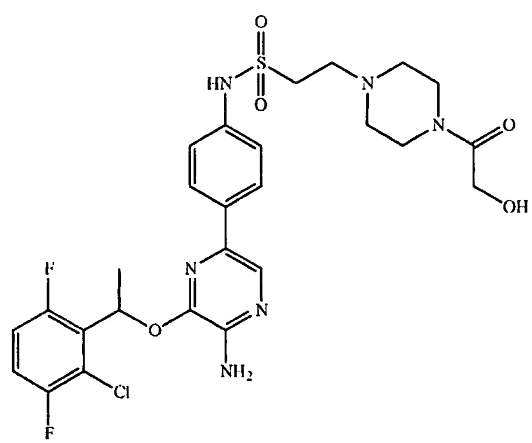
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-119		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide	0.48	4 as in Example II-109	(300 MHZ, CDCl3) δ 8.06(s, 1H), 7.82(m, 4H), 7.00(m, 2H), 6.70(m, 2H), 5.03(s, 2H), 3.62 (m, 4H), 3.50(m, 2H), 2.65(t, 2H), 2.52(m, 4H), 2.10(s, 3H), 1.83(d, 3H).	559
II-120		2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethanesulfonic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.19	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.96(s, 1H), 7.75(d, 2H), 7.24(m, 3H), 7.08(m, 1H), 6.95(m, 1H), 6.70(q, 1H), 5.02(s, 2H), 4.14(s, 2H), 3.64(m, 3H), 3.25 (m, 4H), 2.91(m, 2H), 2.44(m, 4H), 1.83(d, 3H).	611

TABLE 4-continued

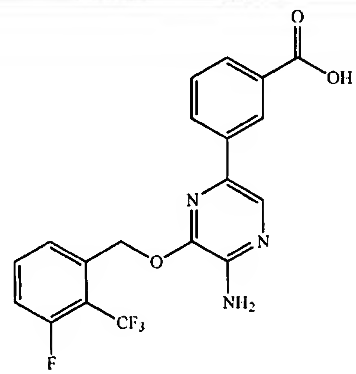
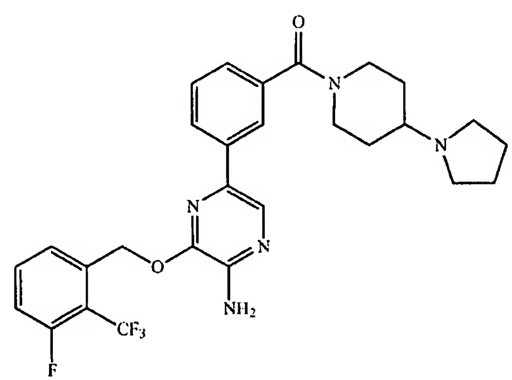
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-121		3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzoic acid		3 as in Example I-211		408
II-122		{3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.19	4 as in Example II-122	(300 MHZ, CDCl3) δ 8.09(s, 1H), 7.88(m, 2H), 7.56(m, 1H), 7.44(t, 1H), 7.34(d, 1H), 7.21(t, 1H), 5.69(s, 2H), 4.92(s, 2H), 4.70(m, 1H), 3.82(m, 1H), 3.06(m, 1H), 2.98(m, 1H), 2.65 (m, 4H), 2.28(m, 1H), 1.02(m, 1H), 1.81(m, 5H), 1.55(m, 2H).	544

TABLE 4-continued

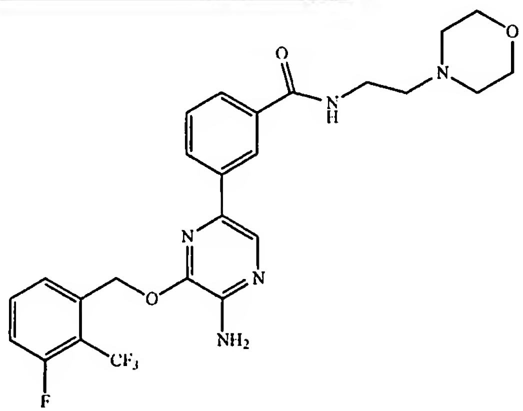
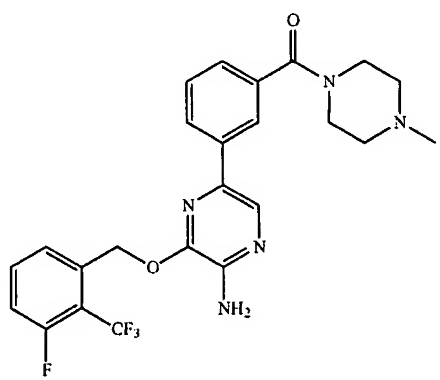
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-123		3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-{2-[ethyl-(2-methoxy-ethyl)-amino]-ethyl}-benzamide	0.45	4 as in Example II-122	(300 MHZ, CDCl3) δ 8.34(s, 1H), 8.14 (s, 1H), 8.01(d, 1H), 7.68(d, 1H), 7.53(m, 1H), 7.50(t, 1H), 7.45(d, 1H), 7.21(t, 1H), 6.79 (bm, 1H), 5.72(s, 2H), 4.92(s, 2H), 3.72(m, 4H), 3.61 (m, 2H), 2.66(m, 2H), 2.55(m, 4H).	520
II-124		{3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzylloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.23	4 as in Example II-122	(300 MHZ, CDCl3) δ 8.10(s, 1H), 7.90(m, 2H), 7.60–7.20(m, 5H), 5.70(s, 2H), 4.91(s, 2H), 3.85(m, 2H), 3.50(m, 2H), 2.52(m, 2H), 2.32 (m, 2H), 2.33(s, 3H).	490

TABLE 4-continued

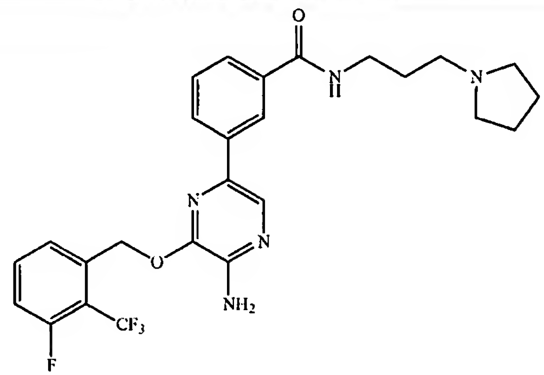
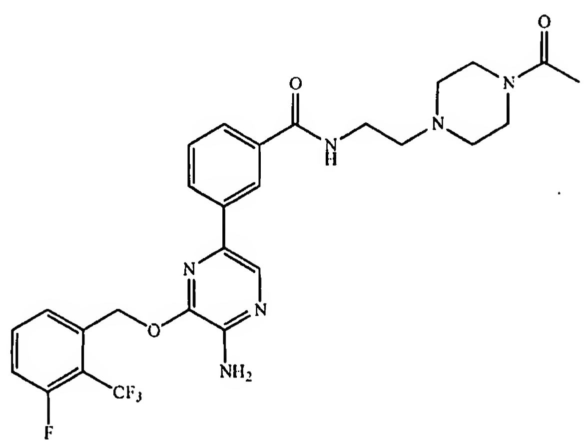
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-125		3-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.22	4 as in Example II-122	(300 MHZ, CDCl3) δ 8.85 (bm, 1H), 8.34(s, 1H), 8.13(s, 1H), 7.95(d, 1H), 7.60(d, 1H), 7.56(m, 1H), 7.45(m, 2H), 7.20(t, 1H), 5.72(s, 2H), 4.92(s, 2H), 3.61(m, 2H), 2.72(m, 2H), 2.57 (m, 4H), 1.82(m, 2H), 1.76(m, 4H).	518
II-126		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-[5-amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-benzamide	0.65	4 as in Example II-122	(300 MHZ, CDCl3) δ 8.28(s, 1H), 8.14 (s, 1H), 7.99(d, 1H), 7.67(d, 1H), 7.58(m, 1H), 7.52(t, 1H), 7.42(d, 1H), 7.22(t, 1H), 6.75 (bm, 1H), 5.72(s, 2H), 4.95(s, 2H), 3.62(m, 4H), 3.47 (m, 2H), 2.63(m, 2H), 2.52(m, 4H), 2.08(s, 3H).	561

TABLE 4-continued

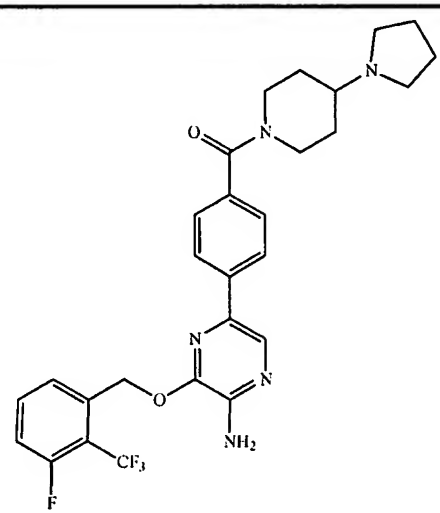
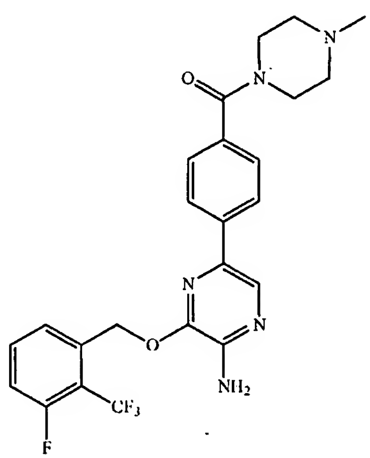
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-127		{4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.047	4 as in Example II-94	(300 MHZ, CDCl3) δ 8.10(s, 1H), 7.88 (d, 2H), 7.52(m, 1H), 7.44(d, 2H), 7.42(m, 1H), 7.20(t, 1H), 5.71(s, 2H), 5.05(s, 2H), 4.62(m, 1H), 3.82(m, 1H), 3.06(m, 1H), 2.98(m, 1H), 2.65 (m, 4H), 2.28(m, 1H), 1.02(m, 1H), 1.81(m, 5H), 1.55(m, 2H).	544
II-128		{4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone	0.15	4 as in Example II-94	(300 MHZ, CDCl3) δ 8.08(s, 1H), 7.88 (d, 2H), 7.55~7.40(m, 4H), 7.21(t, 1H), 5.72(s, 2H), 5.01(s, 2H), 3.82(m, 2H), 3.50(m, 2H), 2.50 (m, 2H), 2.32(m, 2H), 2.33(s, 3H).	490

TABLE 4-continued

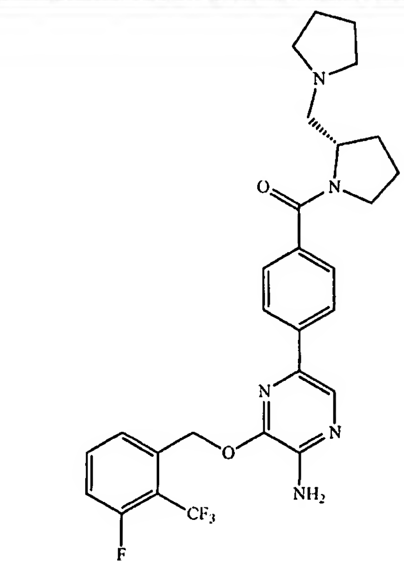
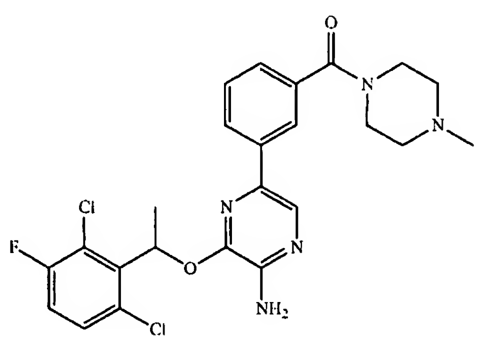
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-129		{4-[5-Amino-6-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-phenyl}-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.052	4 as in Example II-94	(300 MHZ, CDCl3) δ 8.11(s, 1H), 7.88(d, 2H), 7.68(m, 3H), 7.42(d, 1H), 7.22(t, 1H), 5.72(s, 2H), 4.92(s, 2H), 3.50(m, 2H), 3.74(m, 4H), 1.84(d, 3H), 1.57–2.18(m, 11H).	544
II-130		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.17	4 as in Example II-84	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.79(m, 2H), 7.40(t, 1H), 7.29(m, 1H), 7.01(t, 1H), 6.81(q, 1H), 5.06(s, 2H), 3.85(m, 2H), 3.46(m, 2H), 2.51 (m, 2H), 2.35(m, 2H), 2.33(s, 3H), 1.84(d, 3H).	506

TABLE 4-continued

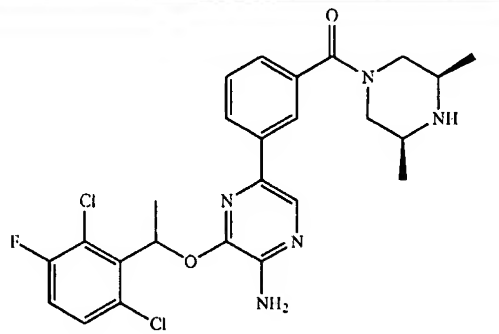
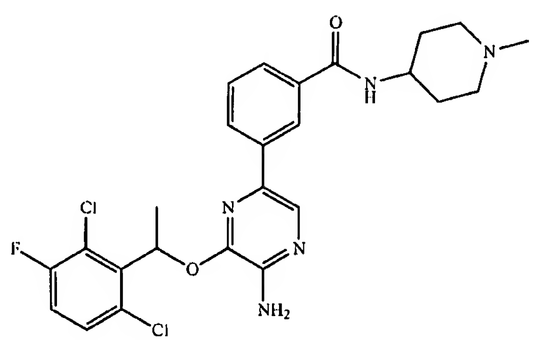
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-131		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.12	4 as in Example II-84	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.78 (m, 2H), 7.39(t, 1H), 7.24(m, 1H), 7.01(t, 1H), 6.81(q, 1H), 5.07(s, 2H), 4.71(m, 1H), 3.58(m, 1H), 2.96(m, 1H), 2.82(m, 1H), 2.66(m, 1H), 2.42 (m, 1H), 1.84(d, 3H), 1.74(m, 1H), 1.22(d, 3H), 1.00(d, 3H).	518
II-132		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.13	4 as in Example II-84	(300 MHZ, CD3OD) δ 8.16(s, 1H), 7.99(s, 1H), 7.82(d, 1H), 7.66(d, 1H), 7.42(m, 2H), 7.15(t, 1H), 6.74(q, 1H), 3.95(m, 1H), 2.98(m, 2H), 2.34(s, 3H), 2.25(m, 2H), 2.01(m, 2H), 1.84 (d, 3H), 1.73(m, 2H).	520

TABLE 4-continued

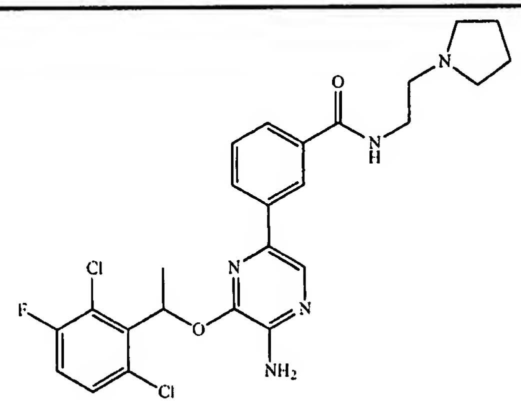
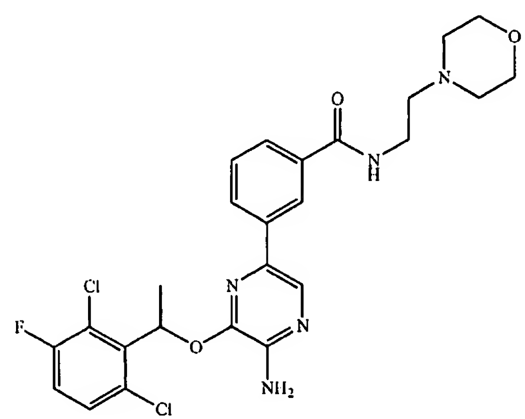
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-133		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.17	4 as in Example II-84	(300 MHZ, CD3OD) δ 8.17(s, 1H), 7.99(s, 1H), 7.82(d, 1H), 7.66(d, 1H), 7.38(m, 2H), 7.12(t, 1H), 6.72(q, 1H), 3.64(m, 2H), 2.86(m, 2H), 2.75 (m, 4H), 2.25(m, 2H), 2.01(m, 2H), 1.84(m, 7H).	520
II-134		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.21	4 as in Example II-84	(300 MHZ, CDCl3) δ 8.13(s, 1H), 8.03(s, 1H), 7.85(d, 1H), 7.67(d, 1H), 7.42(t, 1H), 7.28(dd, 1H), 7.00(t, 1H), 6.86(q, 1H), 6.84 (bm, 1H), 5.11(s, 2H), 3.72(m, 4H), 3.61(m, 2H), 2.63 (m, 2H), 2.53(m, 4H), 1.84(d, 3H).	534

TABLE 4-continued

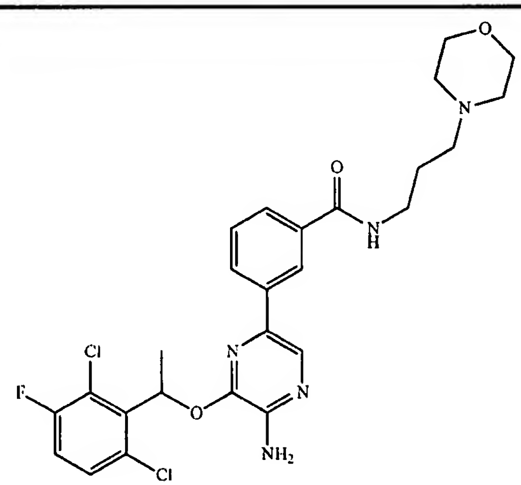
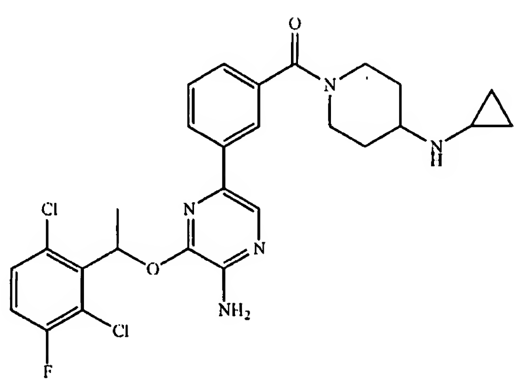
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-135		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-benzamide	0.26	4 as in Example II-84	(300 MHZ, CDCl3) δ 8.19(s, 1H), 8.06(s, 1H), 7.87(d, 1H), 7.70 (bm, 1H), 7.67(d, 1H), 7.42 (t, 1H), 7.28(dd, 1H), 7.01(t, 1H), 6.86(q, 1H), 5.11(s, 2H), 3.64(m, 6H), 2.54(m, 2H), 2.48 (m, 4H), 1.84(m, 5H).	548
II-136		(3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-cyclopropylamino-piperidin-1-yl)-methanone	0.15	4 as in Example II-84		544

TABLE 4-continued

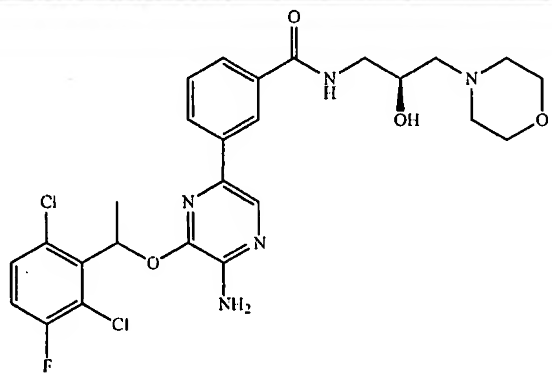
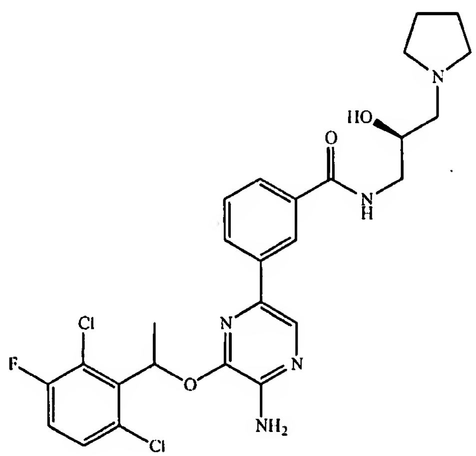
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-137		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((S)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide	0.3	4 as in Example II-84		564
II-138		3-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide	0.13	4 as in Example II-84		548

TABLE 4-continued

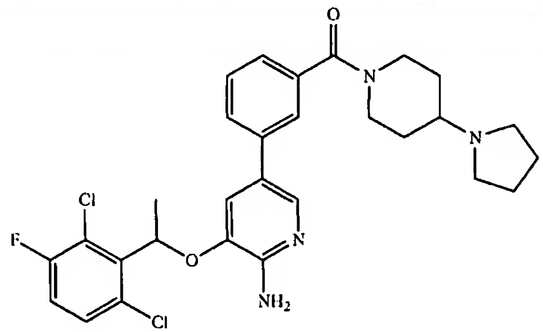
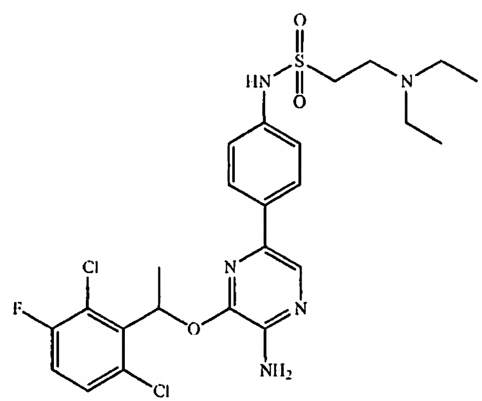
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-139		(3-{6-Amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.071	4 as in Example II-84	(300 MHZ, CDCl3) δ 7.86(s, 1H), 7.41 (m, 3H), 7.30(m, 3H), 7.07(t, 1H), 6.99(s, 1H), 6.12(q, 1H), 4.95(s, 2H), 4.70(m, 1H), 3.82(m, 1H), 3.06(m, 1H), 2.98(m, 1H), 2.65(m, 4H), 2.28 (m, 1H), 1.02(m, 1H), 1.81(m, 5H), 1.55(m, 2H).	559
II-140		2-Diethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.35	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.89(s, 1H), 7.70(d, 2H), 7.28(m, 2H), 7.21(d, 2H), 7.01(t, 1H), 6.82(q, 1H), 5.05(s, 2H), 3.22(m, 2H), 3.00(m, 2H), 2.55(m, 4H), 1.83(d, 3H), 1.60(d, 6H).	556

TABLE 4-continued

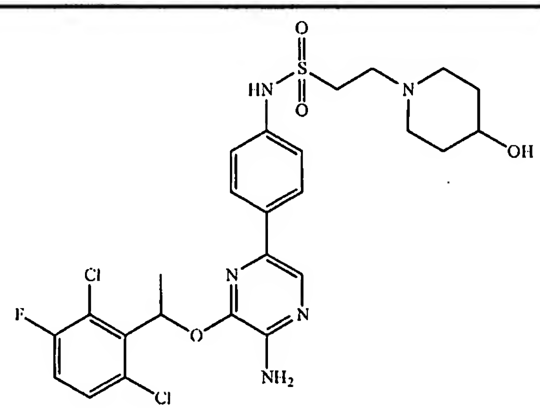
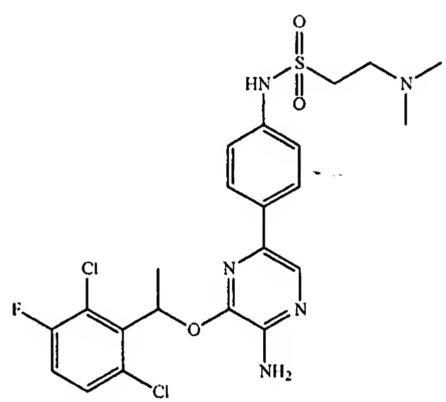
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-141		2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.21	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.95(s, 1H), 7.71(d, 2H), 7.28(m, 2H), 7.21(d, 2H), 7.01(t, 1H), 6.82(q, 1H), 5.00(s, 2H), 3.78(m, 1H), 3.25(t, 2H), 2.90(t, 2H), 2.82(m, 2H), 2.25(m, 2H), 1.90 (m, 2H), 1.84(d, 3H), 1.60(m, 2H).	584
II-142		2-Dimethylamino-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.22	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.89(s, 1H), 7.70(d, 2H), 7.28(m, 2H), 7.21(d, 2H), 7.01(t, 1H), 6.82(q, 1H), 5.05(s, 2H), 3.20(m, 2H), 2.85(m, 2H), 2.28(s, 3H), 1.83(d, 3H).	528

TABLE 4-continued

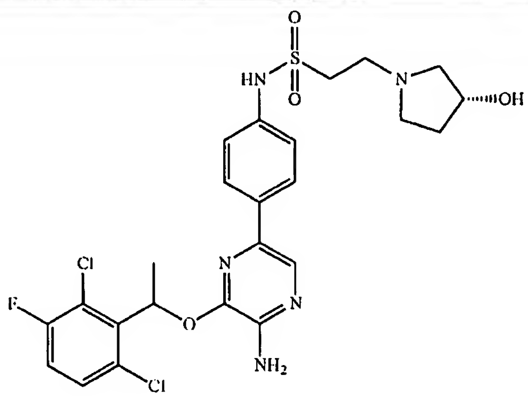
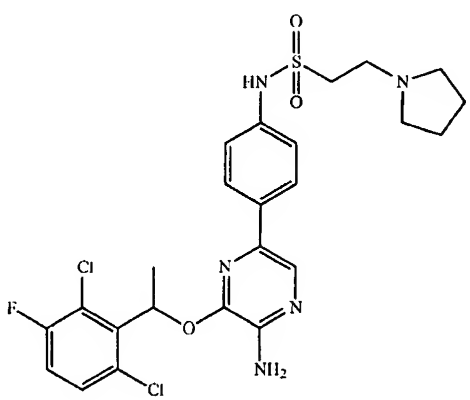
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-143		2-((R)-3-Hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.19	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.93(s, 1H), 7.69(d, 2H), 7.27(m, 4H), 7.00(t, 1H), 6.84(q, 1H), 5.03(s, 2H), 4.43(m, 1H), 3.25(m, 2H), 3.02(m, 3H), 2.84(m, 1H), 2.53(m, 1H), 2.30(m, 1H), 2.22 (m, 1H), 1.84(d, 3H), 1.81(m, 1H).	570
II-144		2-Pyrrolidin-1-ylethanesulfonic acid (4-{5-amino-6-[1-(2,6-dichloro-3-.fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.36	3 as in Example I-243	(300 MHZ, CDCl3) δ 7.94(s, 1H), 7.69(d, 2H), 7.27(m, 2H), 7.19(d, 2H), 7.04(t, 1H), 6.82(q, 1H), 5.01(s, 2H), 3.28(m, 2H), 3.08(m, 2H), 2.60(m, 4H), 1.88(m, 7H).	554

TABLE 4-continued

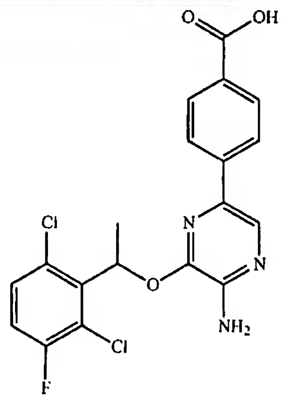
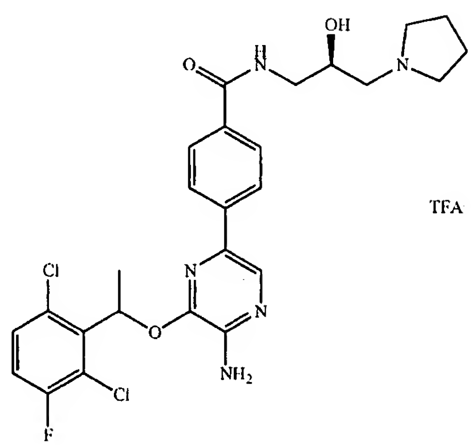
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-145		4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid	1.56	3 as in Example I-211		422
II-146		4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide	0.15	4 as in Example II-146		548

TABLE 4-continued

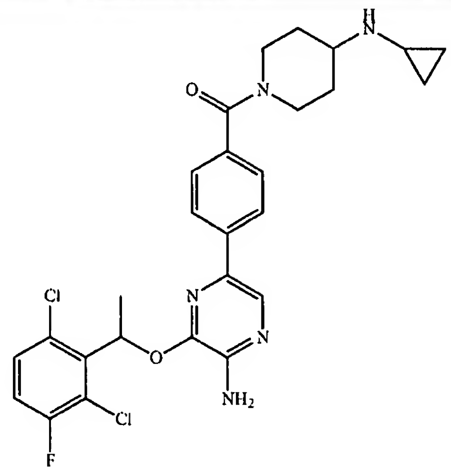
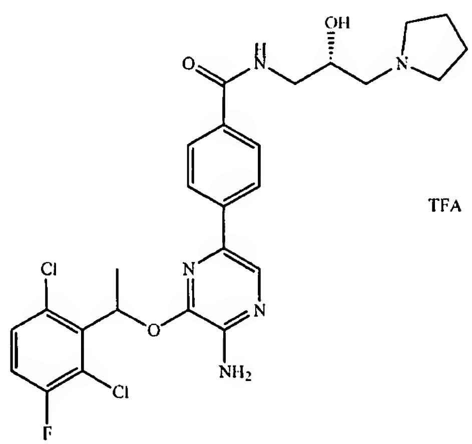
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-147		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-cyclopropylamino-piperidin-1-yl)-methanone	0.13	4 as in Example II-146		544
II-148	 TFA	4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((S)-2-hydroxy-3-pyrrolidin-1-yl-propyl)-benzamide	0.12	4 as in Example II-146		548

TABLE 4-continued

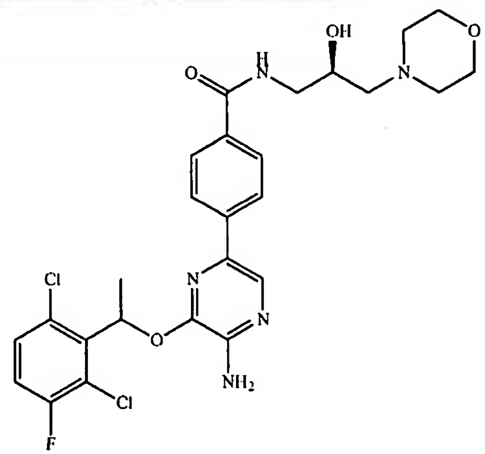
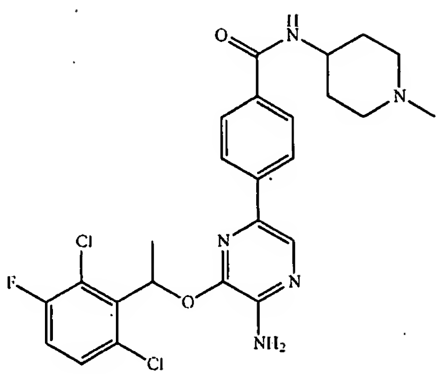
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-149		4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-((R)-2-hydroxy-3-morpholin-4-yl-propyl)-benzamide	0.13	4 as in Example II-146		564
II-150		4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.068	4 as in Example II-146	(300 MHZ, CDCl3) δ 8.01(s, 1H), 7.78(m, 4H), 7.28(m, 1H), 6.95(t, 1H), 6.80(q, 1H), 5.95 (bd, 1H), 5.07(s, 2H), 4.05(m, 1H), 2.85(m, 2H), 2.32(s. 3H), 2.21(m, 2H), 2.08(m, 2H), 1.85(d, 3H), 1.68(m, 2H).	518

TABLE 4-continued

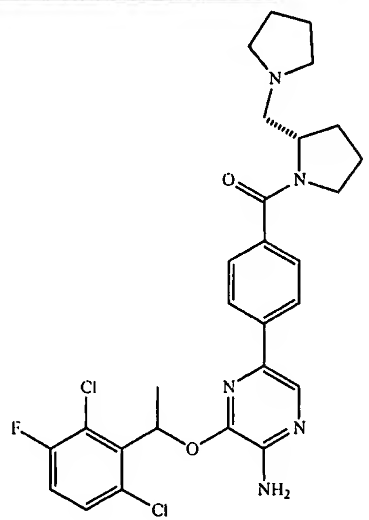
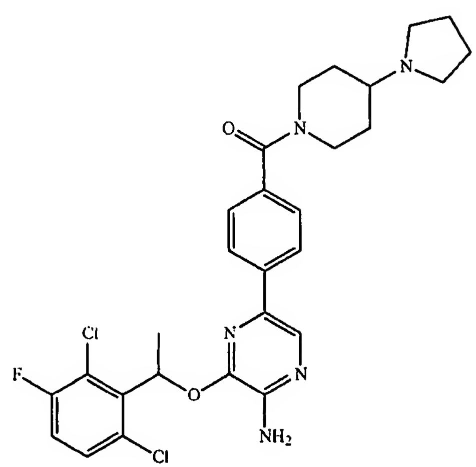
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-151		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.18	4 as in Example II-146	(300 MHZ, CDCl3) δ 8.00(d, 1H), 7.75(d, 2H), 7.51(d, 2H), 7.28(m, 1H), 7.00(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.84(d, 3H), 1.70–2.0(m, 10H)	558
II-152		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.11	4 as in Example II-146	(300 MHZ, CDCl3) δ 7.00(s, 1H), 7.75(d, 2H), 7.40(d, 2H), 7.28(m, 1H), 6.99(t, 1H), 6.76(q, 1H), 5.04(s, 2H), 4.64(m, 1H), 3.84(m, 1H), 3.02(m, 2H), 2.60(m, 4H), 2.30(m, 1H), 1.92 (m, 1H), 1.81(m, 6H), 1.69(m, 2H), 1.62(m, 2H).	558

TABLE 4-continued

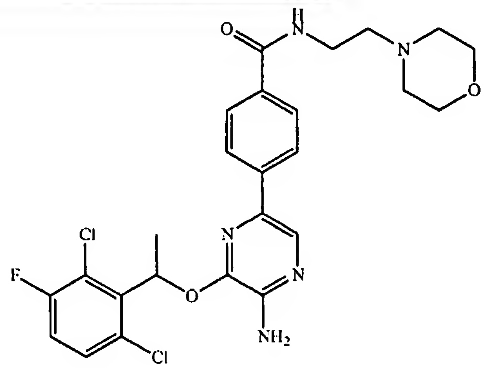
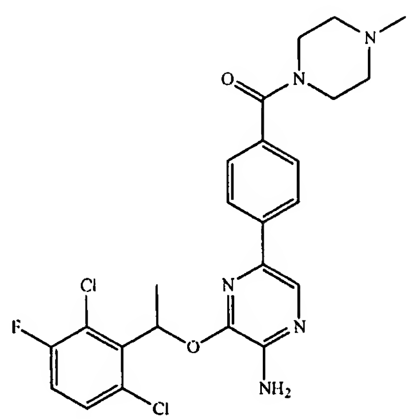
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-153		4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.102	4 as in Example II-146	(300 MHZ, CDCl3) δ 8.05(s, 1H), 7.79(m, 5H), 7.25(m, 1H), 6.95(t, 1H), 6.83(q, 1H), 5.10(s, 2H), 3.74(m, 4H), 3.49(m, 2H), 2.63(m, 2H), 2.52(m, 4H), 1.85(d, 3H).	536
II-154		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.16	4 as in Example II-146	(300 MHZ, CDCl3) δ 7.99(s, 1H), 7.78(d, 2H), 7.43(d, 2H), 7.29(m, 1H), 6.85(t, 1H), 6.94(q, 1H), 5.07(s, 2H), 3.75(m, 2H), 3.50(m, 2H), 2.43(m, 4H), 2.33(s, 3H), 1.84(d, 3H).	506

TABLE 4-continued

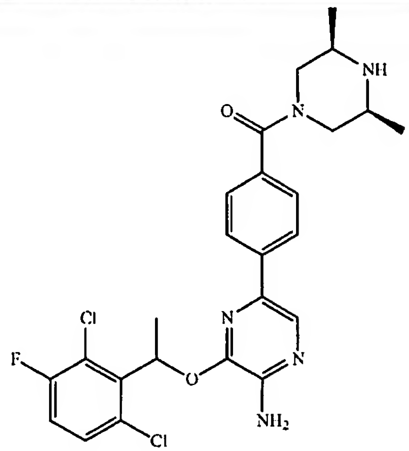
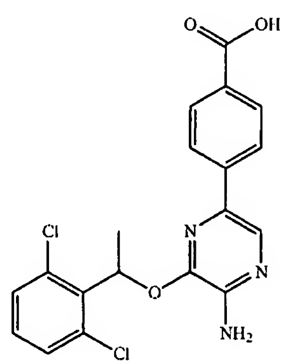
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-155		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.095	4 as in Example II-146	(300 MHZ, CDCl3) δ 8.02(s, 1H), 7.79(d, 2H), 7.40(d, 2H), 7.28(m, 1H), 6.98(t, 1H), 6.84(q, 1H), 5.04(s, 2H), 4.65(m, 1H), 3.56(m, 1H), 2.85(m, 2H), 2.70(m, 1H), 2.44(m, 1H), 1.84 (d, 3H), 1.65(m, 1H), 1.13(m, 3H), 1.00(m, 3H).	518
II-156		4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid		3 as in Example I-211		404

TABLE 4-continued

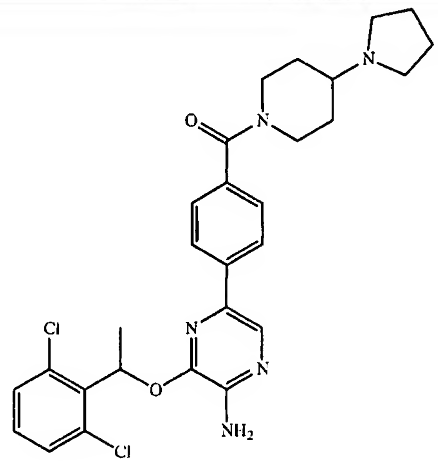
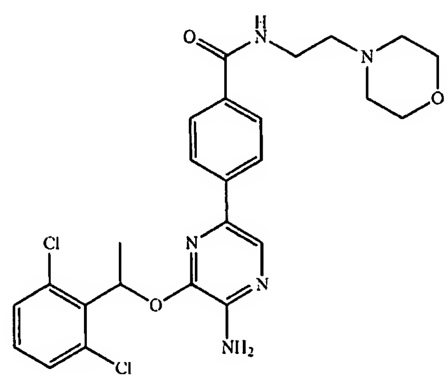
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-157		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.16	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.05(s, 1H), 7.82(d, 2H), 7.50(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 2.98(br, 2H), 2.60(s, 4H), 2.25(br, 2H), 1.89(d, 3H), 1.2–1.98(br, 8H).	540
II-158		4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.32	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.16(s, 1H), 7.89(d, 2H), 7.75(d, 2H), 7.32(m, 2H), 7.15(t, 1H), 6.91(q, 1H), 6.78(m, 1H), 5.10(s, 2H), 3.74(m, 4H), 3.63 (m, 2H), 2.65(m, 2H), 2.54(m, 4H), 1.85(d, 3H).	516

TABLE 4-continued

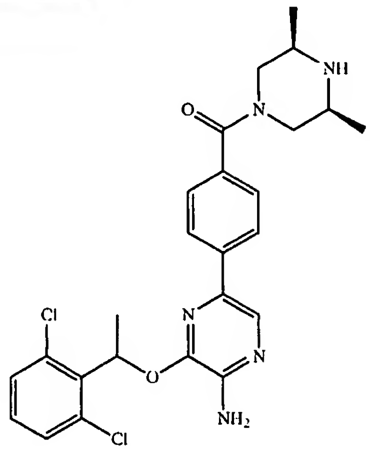
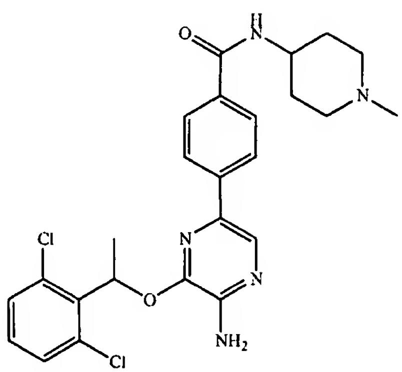
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-159		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.14	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.05(s, 1H), 7.82(d, 2H), 7.50(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 4.60(s, 1H), 4.30(t, 1H), 3.60 (s, 1H), 2.70(m, 4H), 1.89(d, 3H), 0.8–1.2(br, 6H).	500
II-160		4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.12	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.16(s, 1H), 7.90(d, 2H), 7.83(d, 2H), 7.32(t, 2H), 7.16(t, 1H), 6.84(q, 1H), 6.00(d, 1H), 5.08(s, 2H), 4.05(m, 1H), 2.81(m, 2H), 2.35(s, 3H), 2.21(m, 2H), 2.08 (m, 2H), 1.84(d, 3H), 1.60(m, 2H).	500

TABLE 4-continued

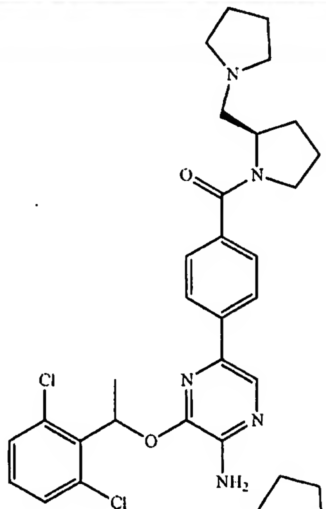
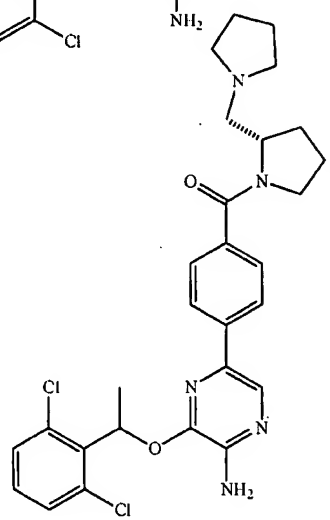
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-161		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.16	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.05(s, 1H), 7.82(d, 2H), 7.50(d, 2H), 7.26(d, 2H), 7.15(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 4.30(t, 1H), 3.50(m, 2H), 2.65(m, 4H), 1.86(d, 3H), 1.70–2.0(m, 10H)	542
II-162		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.14	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.50(s, 1H), 7.82(d, 2H), 7.50(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.86(d, 3H), 1.70–2.0(m, 10H)	542

TABLE 4-continued

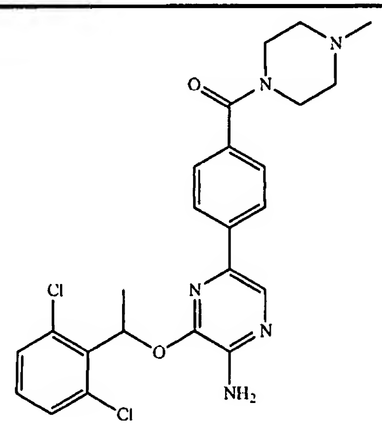
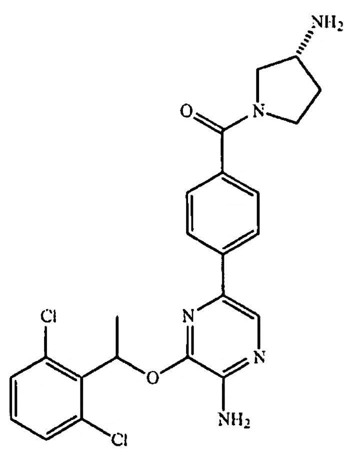
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-163		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.15	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.50(s, 1H), 7.82(d, 2H), 7.50(d, 2H), 7.31(d, 2H), 7.15(t, 1H), 6.90(q, 1H), 5.05(s, 2H), 3.60(m, 4H), 2.45(m, 4H), 2.31(s, 3H), 1.89(d, 3H)	486
II-164		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-aminopyrrolidin-1-yl)-methanone	0.15	4 as in Example II-157	(300 MHZ, CD3OD) δ 7.89(m, 3H), 7.60(m, 2H), 7.40(m, 2H), 7.25(m, 1H), 6.74(m, 1H), 4.90(s, 2H), 4.05–3.60(m, 4H), 3.50(m, 2H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	472

TABLE 4-continued

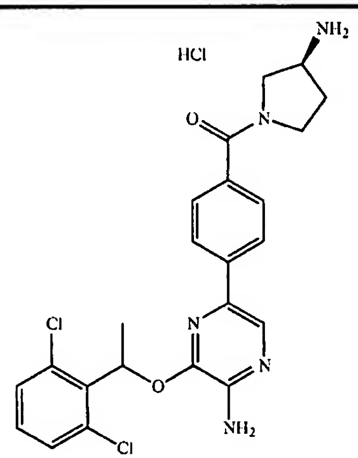
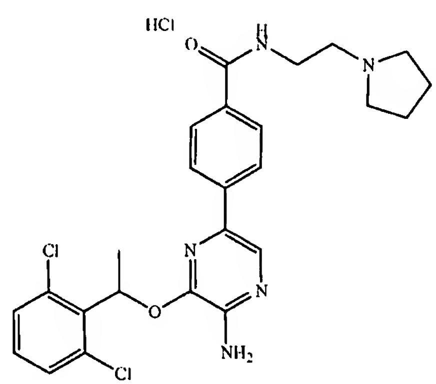
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-165		(4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone hydrogen chloride	0.1	4 as in Example II-157	(300 MHZ, CD3OD) δ 7.89(m, 3H), 7.60(m, 2H), 7.40(m, 2H), 7.25(m, 1H), 6.74(m, 1H), 4.90(s, 2H), 4.05–3.60(m, 4H), 3.50(m, 2H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	472
II-166		4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.11	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.01(s, 1H), 7.80(m, 4H), 7.31(dt, 2H), 7.16(t, 1H), 6.84(m, 2H), 5.04(s, 2H), 3.55(m, 2H), 2.71(m, 2H), 2.57(m, 4H), 1.84(d, 3H), 1.83(m, 4H).	502

TABLE 4-continued

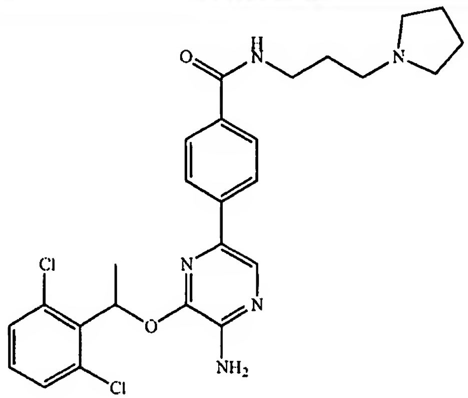
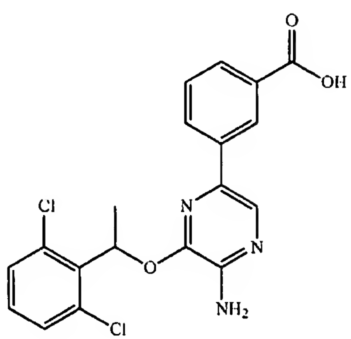
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-167		4-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.22	4 as in Example II-157	(300 MHZ, CDCl3) δ 8.80(s, 1H), 8.10(s, 1H), 7.80(m, 4H), 7.21(d, 2H), 7.16(t, 1H), 6.84(q, 1H), 5.04(s, 2H), 3.55(m, 2H), 2.71(m, 2H), 2.57 (m, 4H), 1.84(m, 4H), 1.83(d, 3H), 1.81(m, 2H).	514
II-168		3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzoic acid		3 as in Example I-211		404

TABLE 4-continued

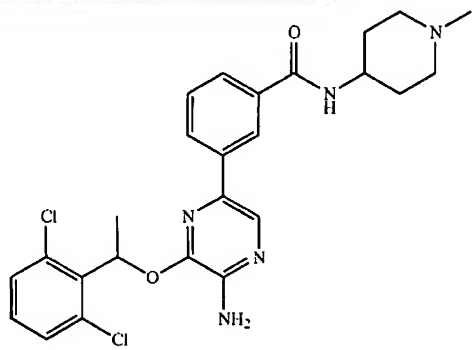
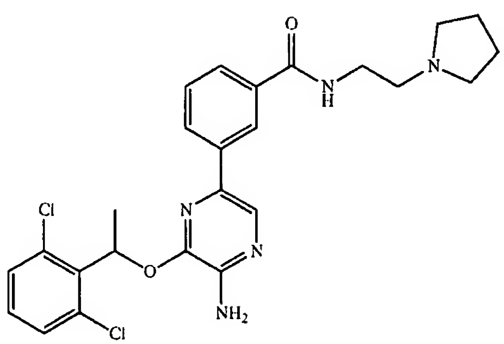
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-169		3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(1-methyl-piperidin-4-yl)-benzamide	0.18	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.16(s, 1H), 8.03(s, 1H), 7.88(d, 1H), 7.70(d, 1H), 7.42(t, 1H), 7.23(d, 2H), 7.10(t, 1H), 6.94(q, 1H), 6.15 (bd, 1H), 5.08(s, 2H), 4.05(m, 1H), 2.91(m, 2H), 2.35 (s, 3H), 2.21(m, 2H), 2.08(m, 2H), 1.84(d, 3H), 1.68(m, 2H).	502
II-170		3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	0.33	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.15(s, 1H), 8.02(s, 1H), 7.85(d, 1H), 7.71(d, 1H), 7.40(t, 1H), 7.28(d, 2H), 7.10(m, 2H), 6.90(q, 1H), 5.10(s, 2H), 3.64 (m, 2H), 2.80(m, 2H), 2.64(m, 4H), 1.85(m, 7H).	500

TABLE 4-continued

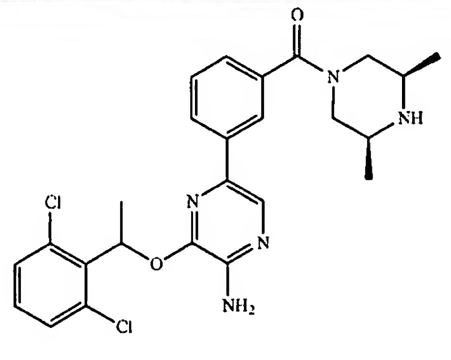
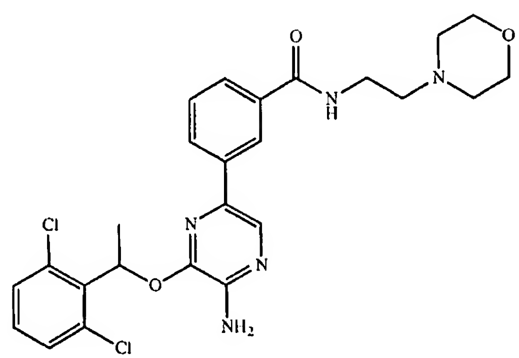
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-171		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.36	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.04(s, 1H), 7.79(m, 2H), 7.40(t, 1H), 7.28(m, 3H), 7.11(t, 1H), 6.86(q, 1H), 5.05(s, 2H), 4.69(m, 1H), 3.56(m, 1H), 2.95(m, 1H), 2.79(m, 1H), 2.71(m, 1H), 2.44 (m, 1H), 1.84(d, 3H), 1.25(d, 3H), 1.17(d, 3H).	500
II-172		3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide	0.48	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.16(s, 1H), 8.03(s, 1H), 7.89(d, 1H), 7.69(d, 1H), 7.43(t, 1H), 7.28(d, 2H), 7.10(t, 1H), 6.91(q, 1H), 6.88(m, 1H), 5.10(s, 2H), 3.74(m, 4H), 3.63(m, 2H), 2.65 (m, 2H), 2.54(m, 4H), 1.85(d, 3H).	516

TABLE 4-continued

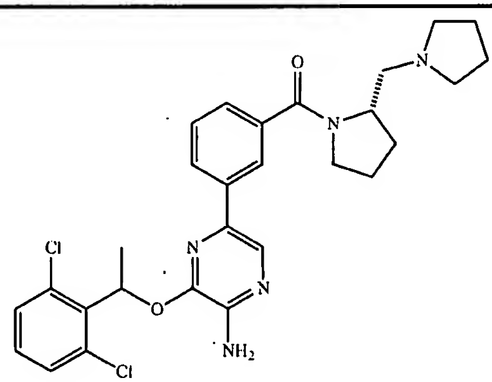
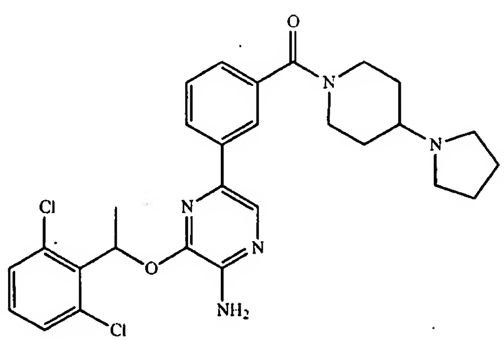
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-173		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.18	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.01(d, 1H), 7.87(m, 2H), 7.37(m, 2H), 7.28(m, 2H), 7.11(t, 1H), 6.90 (m, 1H), 5.05(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.84(d, 3H), 1.70–2.0(m, 10H)	540
II-174		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.17	4 as in Example II-169	(300 MHZ, CDCl3) δ 7.99(s, 1H), 7.78(m, 2H), 7.39(t, 1H), 7.28(m, 3H), 7.08(t, 1H), 6.87(q, 1H), 5.04(s, 2H), 4.64(m, 1H), 3.84(m, 1H), 3.02(m, 2H), 2.60(m, 4H), 2.30(m, 1H), 1.92 (m, 1H), 1.81(m, 6H), 1.69(m, 2H), 1.62(m, 2H).	540

TABLE 4-continued

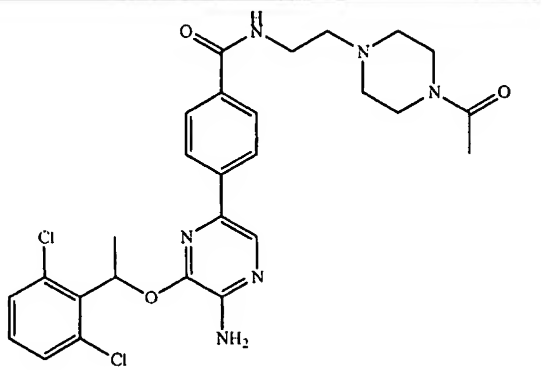
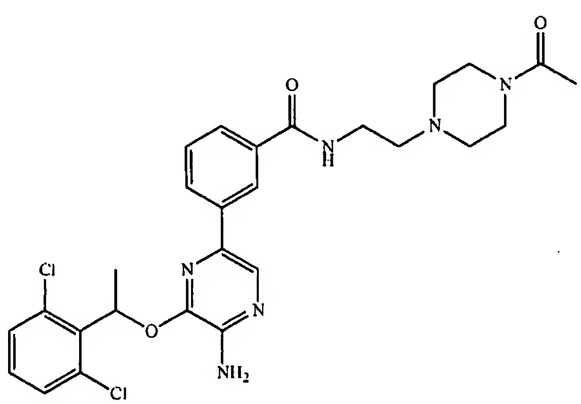
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-175		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-4-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide	0.28	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.06(s, 1H), 7.89(d, 2H), 7.75(d, 2H), 7.31(dt, 2H), 7.11(t, 1H), 6.91(q, 1H), 6.78(m, 1H), 5.12(s, 2H), 4.25(t, 1H), 3.60(m, 3H), 3.45(m, 1H), 2.65(t, 2H), 2.50 (m, 3H), 2.05(s, 2H), 1.85(d, 3H).	559
II-176		N-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-3-{5-amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-benzamide	0.35	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.16(s, 1H), 8.03(s, 1H), 7.99(d, 1H), 7.69(d, 1H), 7.43(t, 1H), 7.28(d, 2H), 7.11(t, 1H), 6.91(q, 1H), 6.78(m, 1H), 5.12(s, 2H), 3.65(m, 4H), 3.49(m, 2H), 2.68 (m, 2H), 2.54(m, 4H), 2.09(s, 3H), 1.85(d, 3H).	559

TABLE 4-continued

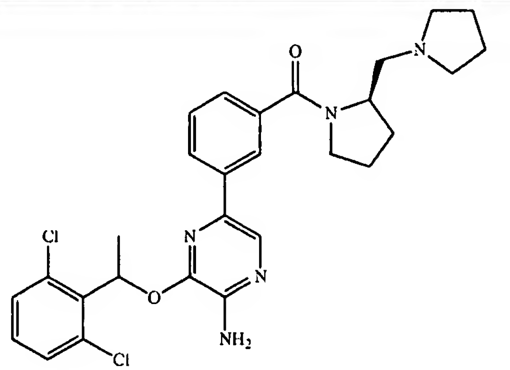
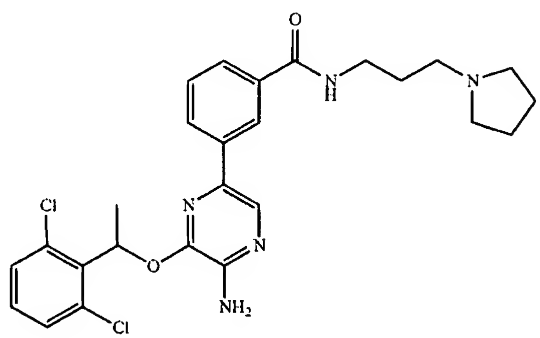
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-177		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.33	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.01(d, 1H), 7.87(m, 2H), 7.37(m, 2H), 7.28(m, 2H), 7.11(t, 1H), 6.90 (m, 1H), 5.05(s, 2H), 4.45(m, 1H), 3.41(m, 2H), 2.70(m, 4H), 1.84(d, 3H), 1.70-2.0(m, 10H)	540
II-178		3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide	0.34	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.48(m, 1H), 8.22(t, 1H), 8.05(s, 1H), 7.91(dt, 1H), 7.66(d, 1H), 7.40(t, 1H), 7.28(d, 2H), 7.10(t, 1H), 6.94(q, 1H), 5.04(s, 2H), 3.62(m, 2H), 2.71(m, 2H), 2.57 (m, 4H), 1.84(d, 3H), 1.83(m, 2H), 1.81(m, 4H).	514

TABLE 4-continued

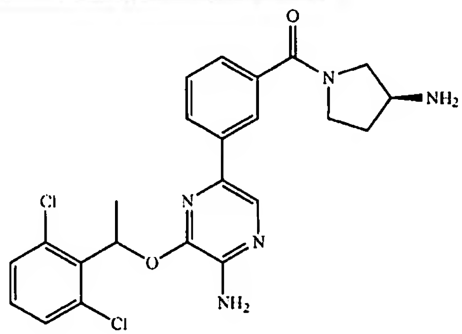
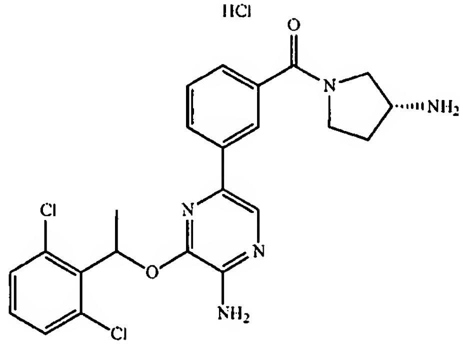
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-179		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((S)-3-amino-pyrroldin-1-yl)-methanone	0.11	4 as in Example II-169	(300 MHZ, CD3OD) δ 7.83(m, 3H), 7.48(m, 2H), 7.37(m, 2H), 7.23(m, 1H), 6.74(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	472
II-180	HCl 	(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone hydrochloride salt	0.18	4 as in Example II-169	(300 MHZ, CD3OD) δ 7.83(m, 3H), 7.48(m, 2H), 7.37(m, 2H), 7.23(m, 1H), 6.74(m, 1H), 4.05–3.60(m, 4H), 3.50(m, 1H), 2.50(m, 1H), 2.18(m, 1H), 1.90(d, 3H).	472

TABLE 4-continued

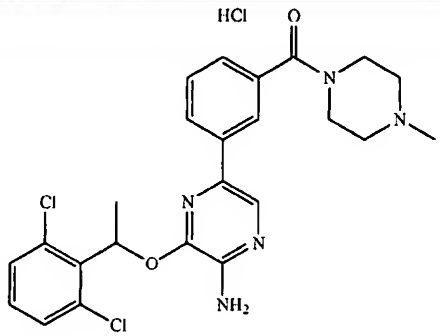
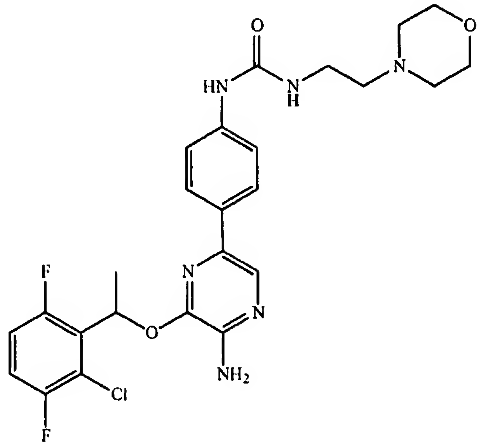
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-181		(3-{5-Amino-6-[1-(2,6-dichloro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone	0.25	4 as in Example II-169	(300 MHZ, CDCl3) δ 8.00(s, 1H), 7.80(m, 2H), 7.40(t, 1H), 7.28(m, 3H), 7.11(t, 1H), 6.87(q, 1H), 5.05(s, 2H), 4.64(m, 1H), 3.87(m, 2H), 3.45(m, 2H), 2.53(m, 2H), 2.36(m, 1H), 2.34 (s, 3H), 1.84(d, 3H).	486
II-182		1-(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea	0.18	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.93(s, 1H), 7.68(d, 2H), 7.38(s, 2H), 6.95(m, 4H), 6.70(q, 1H), 4.94(s, 2H), 3.75(m, 4H), 3.46(m, 2H), 2.69(m, 4H), 2.25(m, 2H), 1.85(d, 3H).	534

TABLE 4-continued

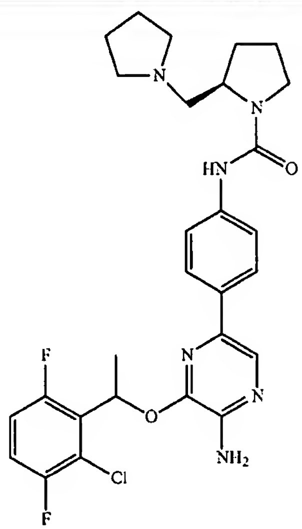
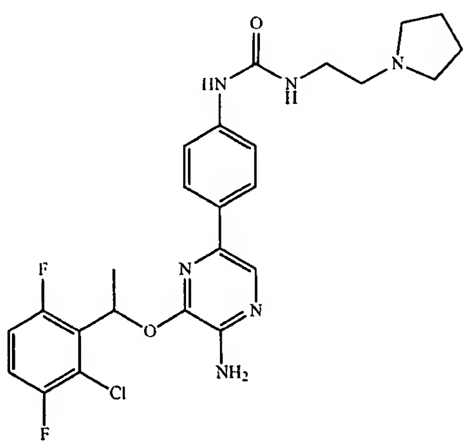
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-183		(R)-2-Pyrrolidin-1-ylmethyl-pyrrolidin-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.21	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.83(s, 1H), 7.40(d, 2H), 7.27(d, 2H), 6.95(m, 3H), 5.95(q, 1H), 4.85(s, 2H), 3.85(m, 1H), 3.75(m, 1H), 3.40(m, 1H), 2.90(m, 4H), 2.65(m, 4H), 2.10(m, 3H), 1.85 (d, 3H), 1.9–1.7(m, 3H).	557
II-184		1-(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea	0.18	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.91(s, 1H), 7.80 (bs, 1H), 7.69(d, 2H), 7.46(d, 2H), 7.35 (bm, 1H), 7.05 (m, 2H), 6.72(q, 1H), 4.86(s, 2H), 3.58(m, 2H), 3.19(m, 4H), 3.12(m, 2H), 2.16(m, 4H), 2.51(s, 3H), 1.81(d, 3H).	517

TABLE 4-continued

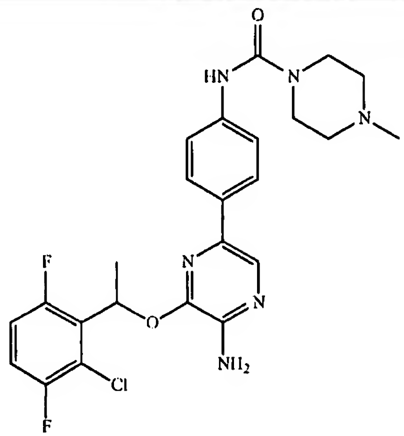
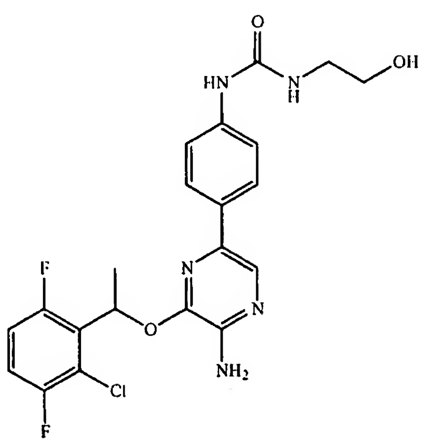
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-185		4-Methyl-piperazin-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.1	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.95(s, 1H), 7.69(d, 2H), 7.39(d, 2H), 7.01-6.91(m, 2H), 6.70(m, 2H), 4.90(s, 2H), 3.61(m, 4H), 2.58(m, 4H), 2.41 (s, 3H), 1.81(d, 3H).	503
II-186		1-(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea	0.21	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.78(s, 1H), 7.60(d, 2H), 7.35(d, 2H), 7.15(m, 4H), 6.55(q, 1H), 4.86 (s, 2H), 3.64(t, 2H), 3.31(t, 3H), 1.82(d, 3H).	464

TABLE 4-continued

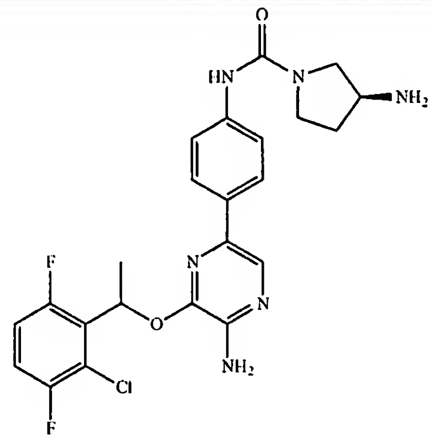
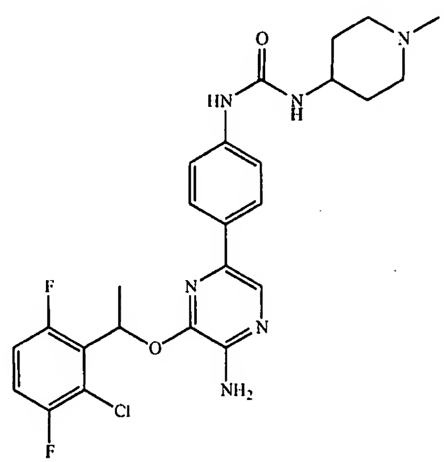
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-187		(S)-3-Amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.082	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.71(s, 1H), 7.65(d, 2H), 7.53(d, 2H), 7.15(m, 3H), 6.77(m, 1H), 4.87 (s, 2H), 3.95(m, 1H), 3.80(m, 1H), 3.65(m, 2H), 3.31(m, 2H), 2.57(m, 1H), 2.20(m, 1H), 1.95(d, 3H).	489
II-188		1-(4-{5-Amino-6-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea	0.054	10 as in Example I-371		517

TABLE 4-continued

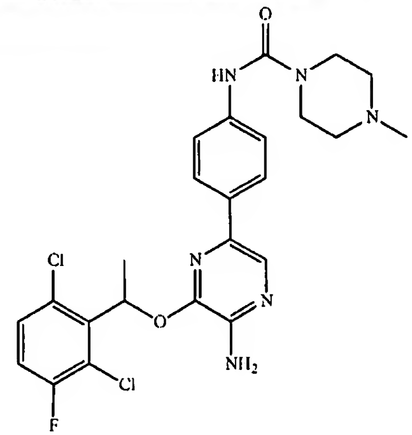
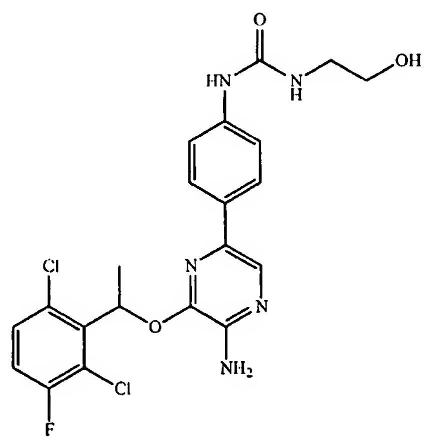
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-189		4-Methyl-piperazine-1-carboxylic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	0.074	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.94(s, 1H), 7.66(d, 2H), 7.37(d, 2H), 7.24(m, 1H), 6.95(t, 1H), 6.81(m, 2H), 4.95(s, 2H), 3.68(m, 4H), 2.73(m, 4H), 2.51(s, 3H), 1.83(d, 3H).	519
II-190		1-(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea	0.28	10 as in Example I-371	(300 MHZ, CDCl3) δ 7.84(s, 1H), 7.60(m, 4H), 7.33(m, 3H), 7.15(m, 1H), 6.70(q, 1H), 4.86 (s, 2H), 3.64(t, 2H), 3.31(m, 3H), 1.82(d, 3H).	480

TABLE 4-continued

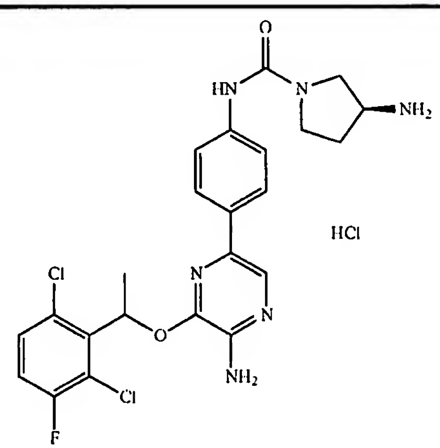
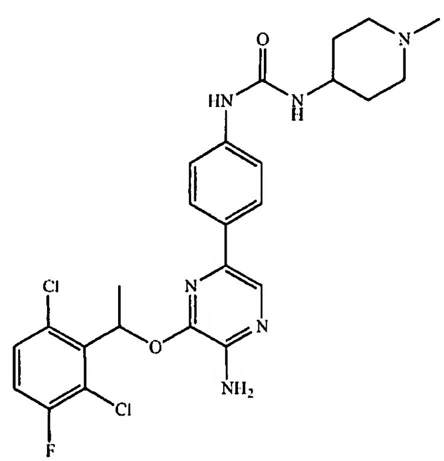
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-191	 HCl	(S)-3-Amino-pyrrolidine-1-carboxylic acid (4-{5-amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-amide	3	10 as in Example I-371		502
II-192		1-(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea	0.052	10 as in Example I-371		535

TABLE 4-continued

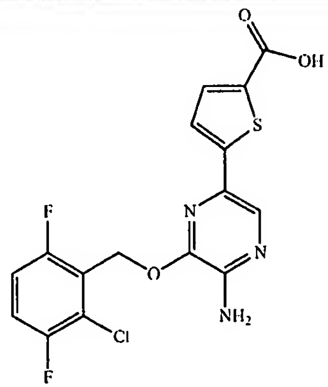
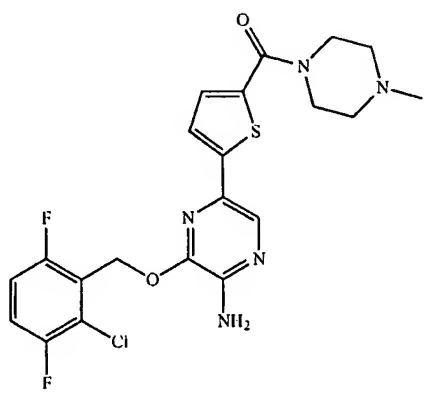
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-193		5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid		3 as in Example I-270		398
II-194		{5-[Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-(4-methyl-piperazin-1-yl)-methanone	0.62	4 as in Example II-194	(300 MHZ, CDCl3) δ 8.01(s, 1H), 7.35(s, 1H), 7.27(s, 1H), 7.15(m, 1H), 6.98(m, 1H), 5.63 (s, 1H), 4.87(m, 1H), 3.80(m, 4H), 2.48(m, 4H), 2.34(s, 3H).	480

TABLE 4-continued

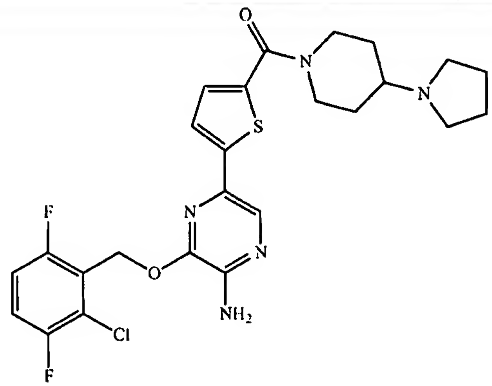
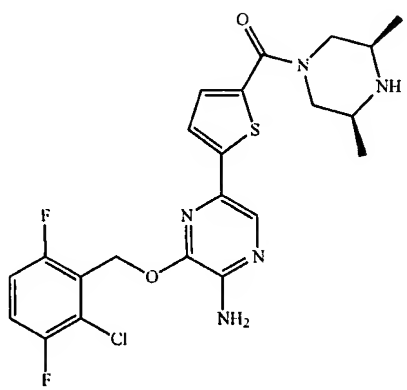
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-195		{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone	0.51	4 as in Example II-194	(300 MHZ, CDCl3) δ 8.01(s, 1H), 7.35(d, 1H), 7.24(d, 1H), 7.15(m, 1H), 6.98(m, 1H), 5.63 (s, 2H), 4.88(m, 2H), 4.42(m, 4H), 3.05(t, 4H), 2.63(m, 2H), 2.35(m, 1H), 2.00(m, 2H), 1.82 (m, 2H), 1.60(m, 2H).	534
II-196		{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone	0.55	4 as in Example II-194	(300 MHZ, CDCl3) δ 8.01(s, 1H), 7.35(d, 1H), 7.24(d, 1H), 7.07(m, 1H), 7.01(m, 1H), 5.63 (s, 2H), 4.88(m, 2H), 4.35(m, 2H), 2.93(m, 2H), 2.60(m, 2H), 1.10(d, 6H).	494

TABLE 4-continued

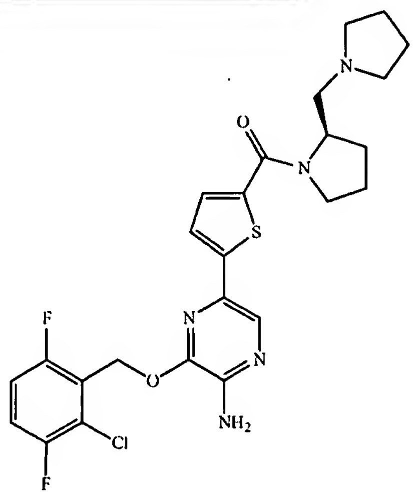
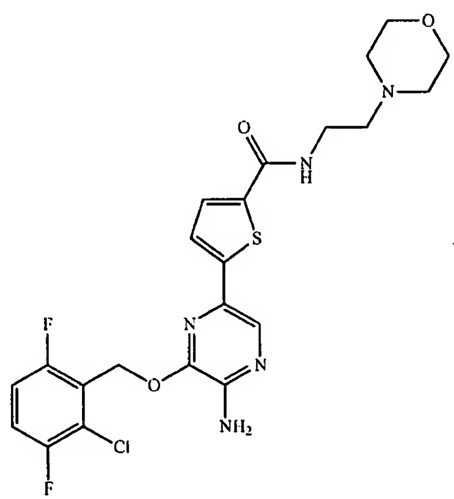
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-197		{5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophen-2-yl}-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone	0.8	4 as in Example II-194	(300 MHZ, CDCl3) δ 8.03(s, 1H), 7.52(d, 1H), 7.38(d, 1H), 7.07(m, 1H), 7.01(m, 1H), 5.63 (s, 2H), 4.88(m, 2H), 4.5-0.80(m, 17H).	534
II-198		5-[5-Amino-6-(2-chloro-3,6-difluoro-benzyloxy)-pyrazin-2-yl]-thiophene-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	0.7	4 as in Example II-194	(300 MHZ, CDCl3) δ 8.03(s, 1H), 7.45(d, 1H), 7.38(d, 1H), 7.20(m, 1H), 7.05(m, 1H), 6.58 (m, 1H), 5.65(s, 2H), 4.89(m, 2H), 3.75(m, 4H), 3.55(m, 2H), 2.61(m, 2H), 2.50(m, 4H)	510

TABLE 4-continued

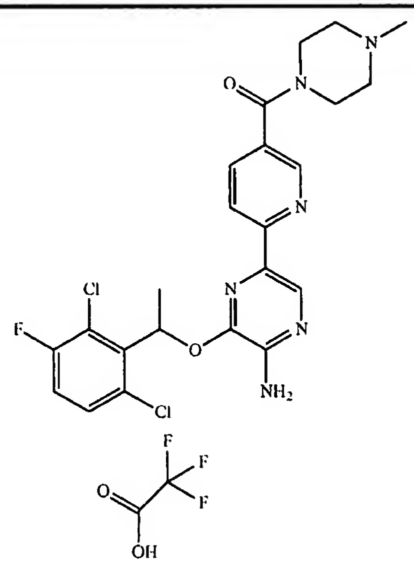
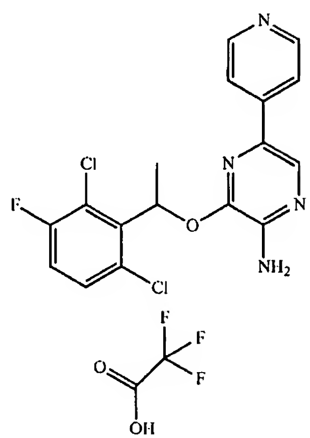
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-199		3-[1-(2,6-dichloro-3-fluoro-phenyl)ethoxy]-5-{5-[(4-methylpiperazin-1-yl)carbonyl]-pyridin-2-yl}pyrazin-2-amine trifluoroacetate	0.15	4 as in Example II-194	(DMSO-d6 + TFA/300 MHz) δ 8.64(s, 1H), 8.29 (s, 1H), 7.96(d, 1H), 7.81(d, 1H), 7.51(m, 1H), 7.35(m, 1H), 6.63(q, 1H), 4.69–4.25(m, 1H), 4.08–3.69(m, 1H), 3.58–3.01(m, 6H), 2.82(s, 3H), 1.84(d, 3H).	505
II-200		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-pyridin-4-yl-pyrazin-2-ylamine	0.045	3		379

TABLE 4-continued

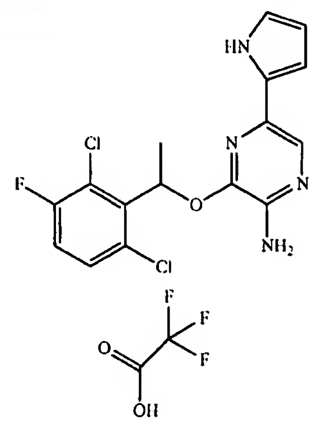
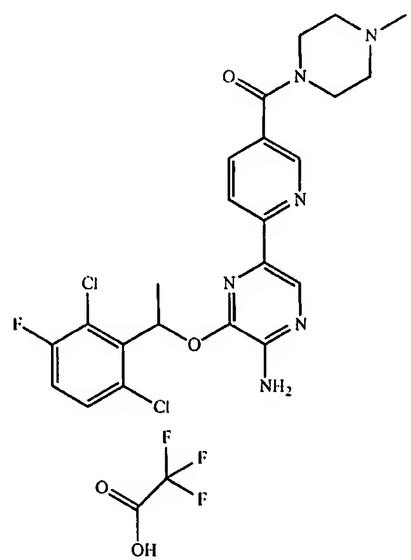
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-201		3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrrol-2-yl)-pyrazin-2-ylamine	0.22	3		367
II-202		(6-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-methanone	0.15	16 as in Example I-488		505

TABLE 4-continued

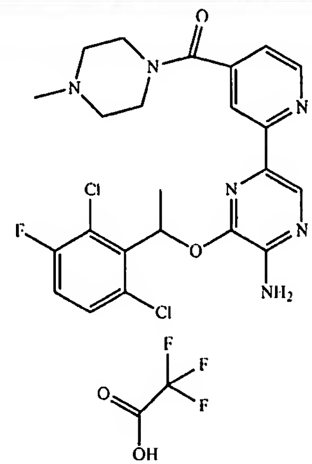
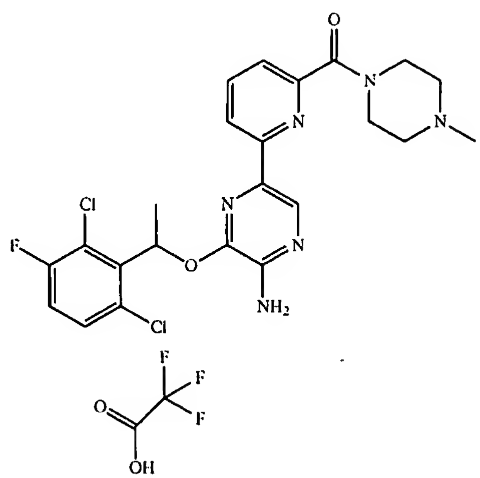
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-203		(2-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-4-yl)-(4-methyl-piperazin-1-yl)-methanone	0.18	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 8.68(d, 1H), 8.34 (s, 1H), 7.62(s, 1H), 7.52–7.27(m, 3H), 6.57(q, 1H), 4.66(m, 1H), 3.70–2.91(m, 7H), 2.86(s, 3H), 1.82(d, 3H).	505
II-204		(6-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone	0.22	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 8.24(s, 1H), 7.96 (dd, 1H), 7.79(d, 1H), 7.53(m, 2H), 7.35(dd, 1H), 6.61(q, 1H), 4.60(br, 1H), 4.12(br, 1H), 3.61–3.30(m, 3H), 3.24–3.04(m, 3H), 2.83(s, 3H), 1.84(d, 3H).	505

TABLE 4-continued

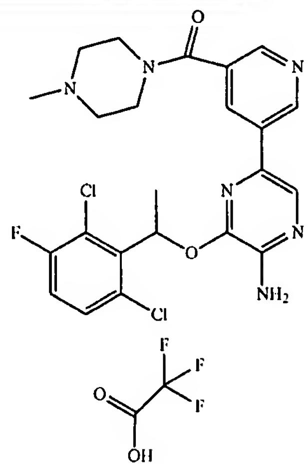
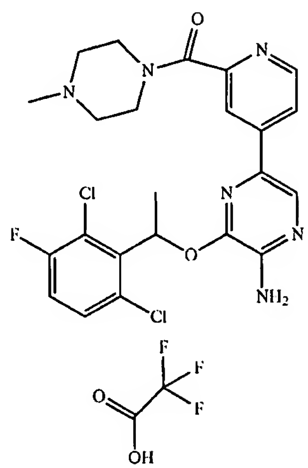
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-205		(5-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-methyl-piperazin-1-yl)-methanone	0.1	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.07(s, 1H), 8.77 (s, 1H), 8.44(s, 1H), 8.31(s, 1H), 7.53(br, 1H), 7.44(m, 1H), 7.32(m, 1H), 6.58(q, 1H), 4.63 (br, 1H), 3.74(br, 1H), 3.61–3.15(m, 4H), 3.06 (m, 2H), 2.83(s, 3H), 1.81(d, 3H).	505
II-206		(4-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone	0.1	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 8.63(d, 1H), 8.39 (s, 1H), 8.01(s, 1H), 7.93(d, 1H), 7.43(m, 1H), 7.28(dd, 1H), 6.58(q, 1H), 4.63(m, 1H), 3.92 (m, 1H), 3.64–3.13(m, 4H), 3.11–2.96(m, 2H), 2.84(s, 3H), 1.81(d, 3H).	505

TABLE 4-continued

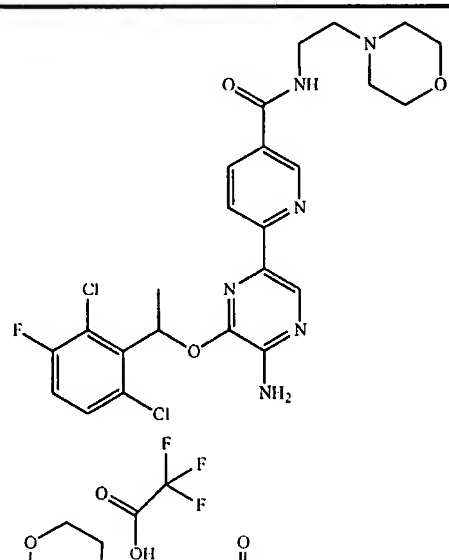
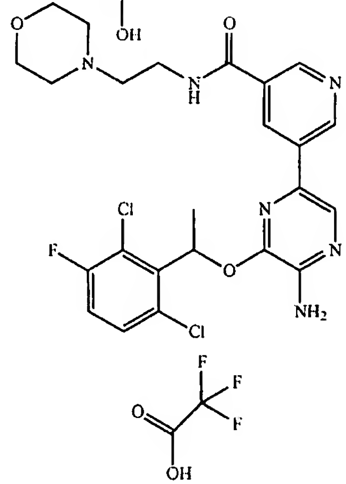
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-207		6-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide		16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.76 (br, 1H), 8.96(m, 2H), 8.37(s, 1H), 8.26(d, 1H), 7.80(d, 1H), 7.51(m, 1H), 7.37(dd, 1H), 6.61(q, 1H), 4.00(d, 2H), 3.74–3.50(m, 6H), 3.34(m, 2H), 3.16(m, 2H), 1.83(d, 3H).	535
II-208		5-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(2-morpholin-4-yl-ethyl)-nicotinamide	0.038	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.16(m, 1H), 9.09(s, 1H), 9.03(s, 1H), 8.83(s, 1H), 8.28(s, 1H), 7.47(m, 1H), 7.32(dd, 1H), 6.66(q, 1H), 4.00(d, 2H), 3.77–3.50(m, 6H), 3.35(m, 2H), 3.16(m, 2H), 1.83(d, 3H).	535

TABLE 4-continued

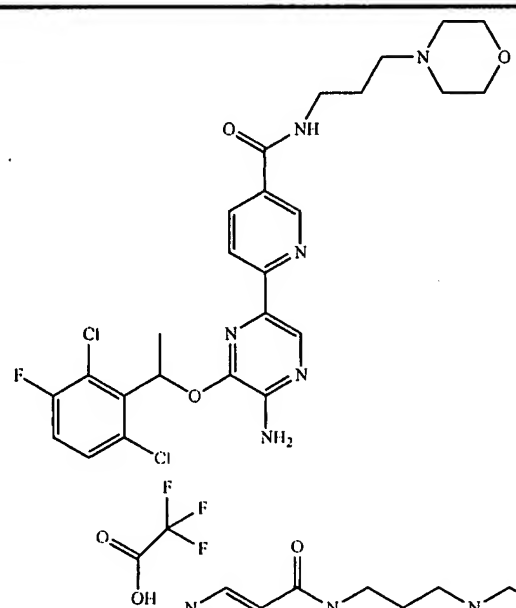
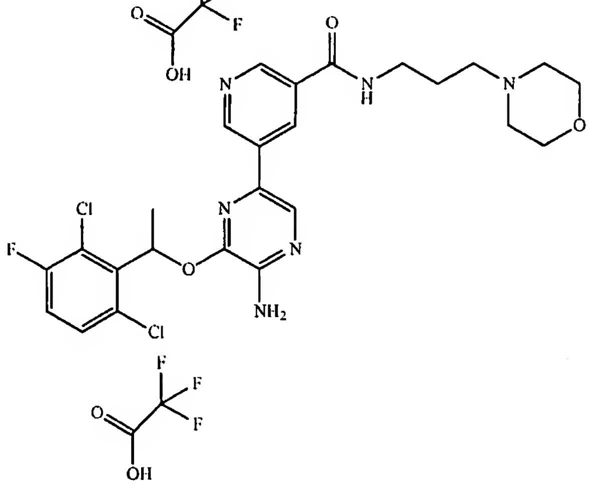
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^{1}H-NMR	MS m/z (M + 1)
II-209		6-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide		16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.74(br, 1H), 8.97 (s, 1H), 8.84(m, 1H), 8.36(s, 1H), 8.26(d, 1H), 7.79(d, 1H), 7.50(m, 1H), 7.37(dd, 1H), 6.61(q, 1H), 3.97(d, 2H), 3.64(t, 2H), 3.50–3.30(m, 4H), 3.23–2.98(m, 4H), 1.92(m, 2H), 1.83(d, 3H).	549
II-210		5-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-N-(3-morpholin-4-yl-propyl)-nicotinamide	0.022	16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.88(br, 1H), 8.86(s, 1H), 8.30(s, 1H), 7.68–7.40(m, 2H), 7.32(m, 1H), 6.67(q, 1H), 3.97(d, 2H), 3.66(t, 2H), 3.43(m, 4H), 3.25–2.97(m, 4H), 1.96(br, 2H), 1.83(d, 3H).	549

TABLE 4-continued

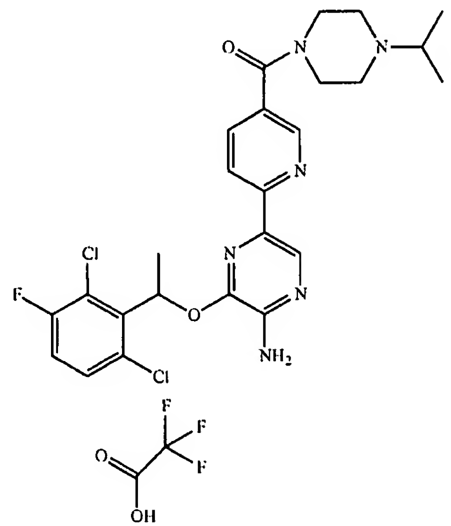
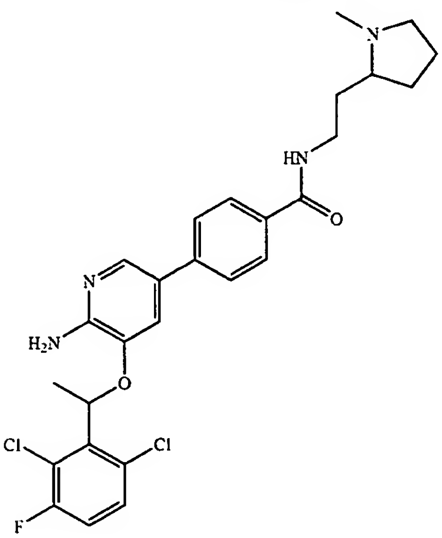
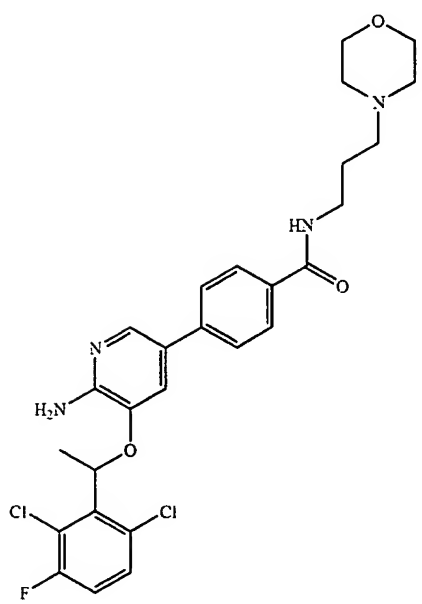
No.	Structure	Name	Met IC_{50} (μM)	Procedure	^1H-NMR	MS m/z (M + 1)
II-211		(6-{5-Amino-6-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyrazin-2-yl}-pyridin-3-yl)-(4-isopropyl-piperazin-1-yl)-methanone		16 as in Example I-488	(DMSO-d6 + TFA/300 MHz) δ 9.70(br, 1H), 8.65(s, 1H), 8.38(s, 1H), 7.95(d, 1H), 7.80(d, 1H), 7.53(m, 1H) 7.39(dd, 1H), 6.62(q, 1H), 4.57(br, 1H), 3.85(br, 1H), 3.60-3.05(m, 7H), 1.83(d, 3H), 1.26(d, 6H).	533

TABLE 5

Section A: Examples L-1 to L-16

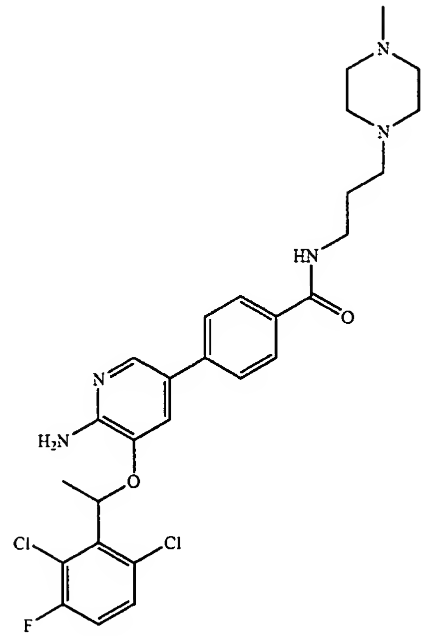


% inhibition = 58

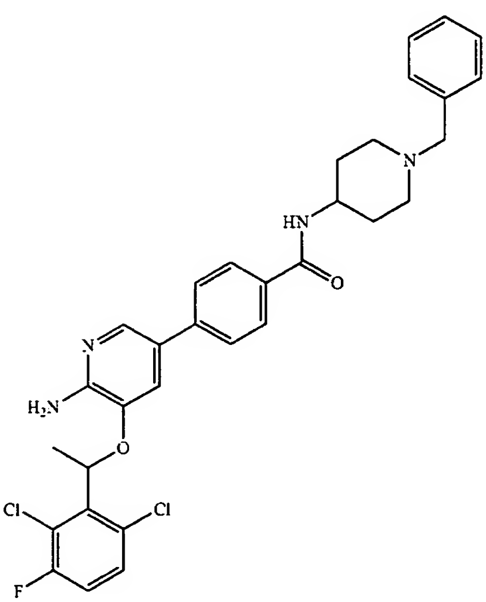


% inhibition = 59

TABLE 5-continued

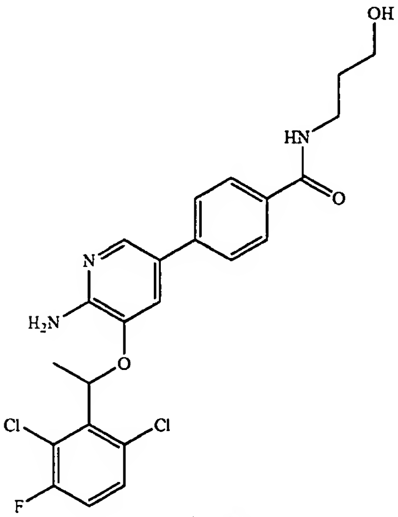


% inhibition = 63

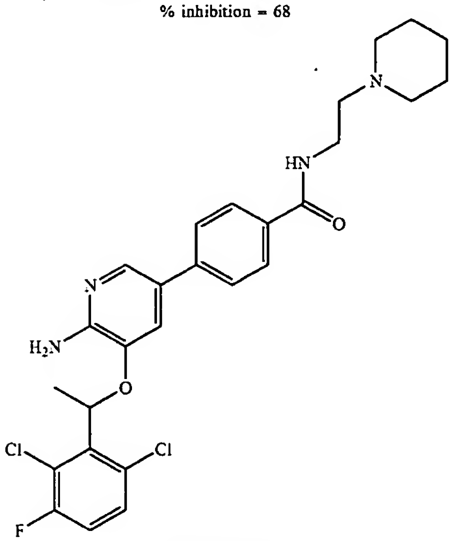


% inhibition = 47

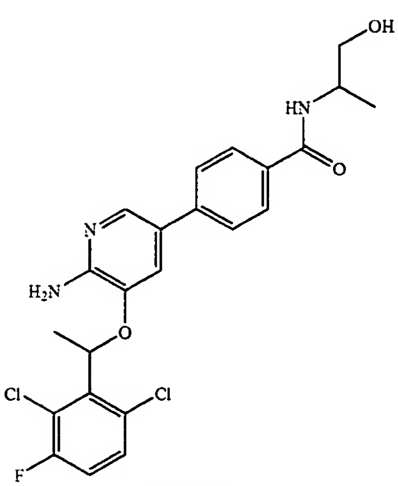
TABLE 5-continued



% inhibition = 68

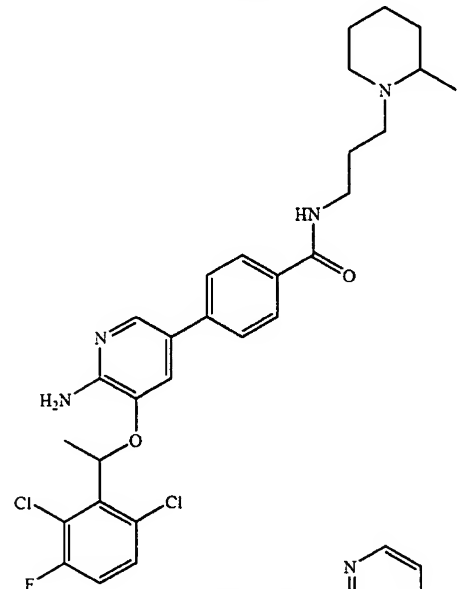


% inhibition = 69

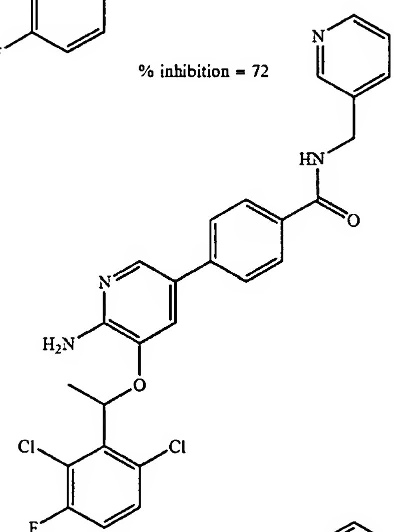


% inhibition = 66

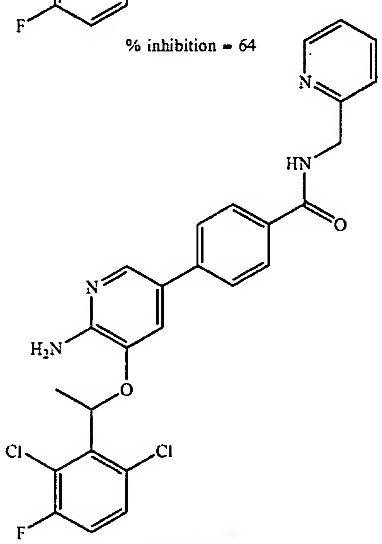
TABLE 5-continued



% inhibition = 72

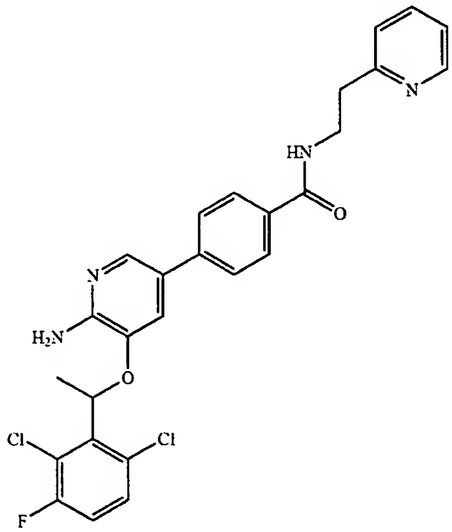


% inhibition = 64

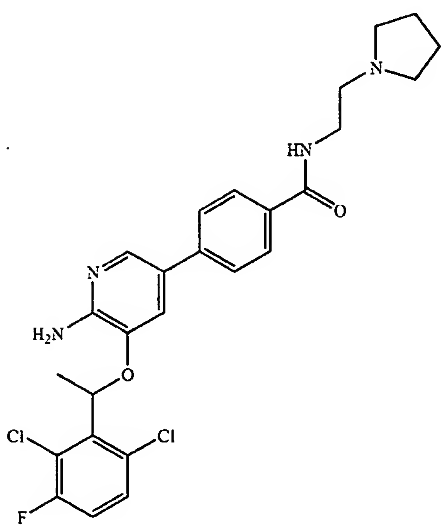


% inhibition = 67

TABLE 5-continued

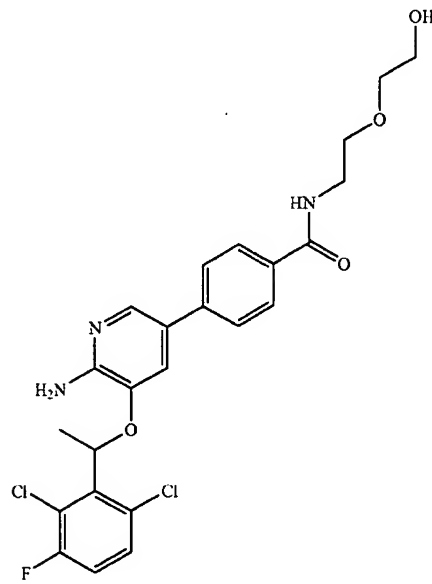


% inhibition = 67

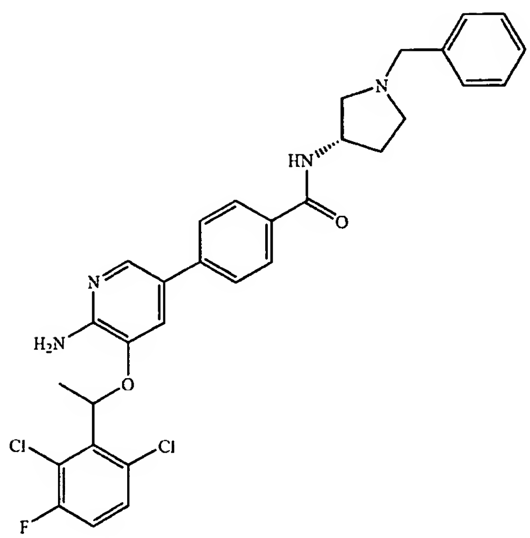


% inhibition = 82

TABLE 5-continued

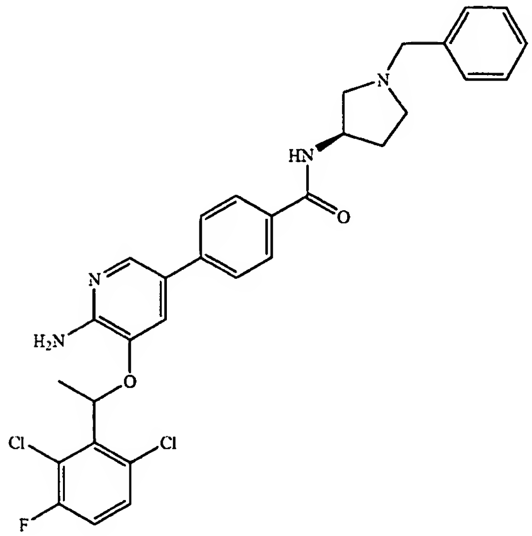


% inhibition = 76

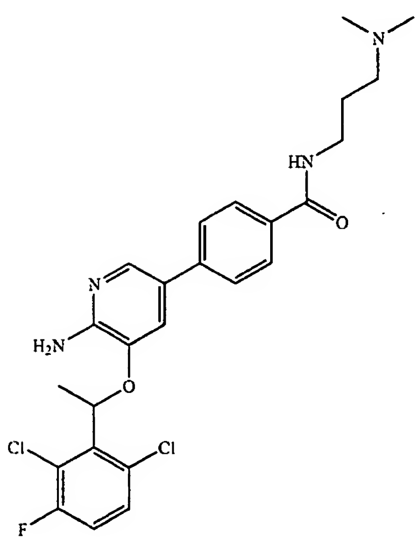


% inhibition = 72

TABLE 5-continued



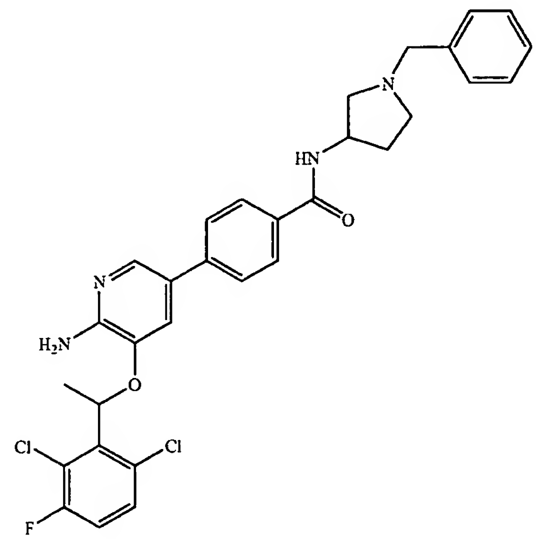
% inhibition = 67



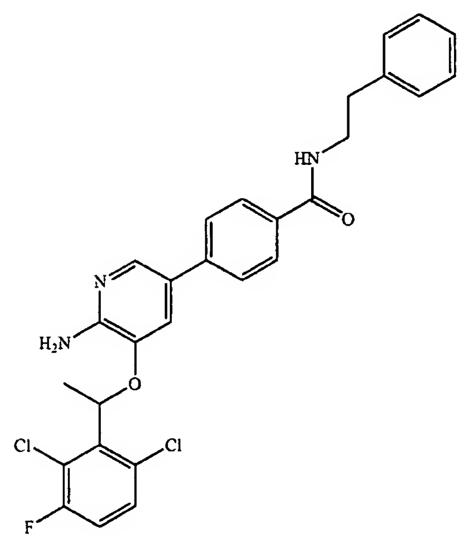
% inhibition = 83

TABLE 5-continued

Section B: Examples L-17 to L-32

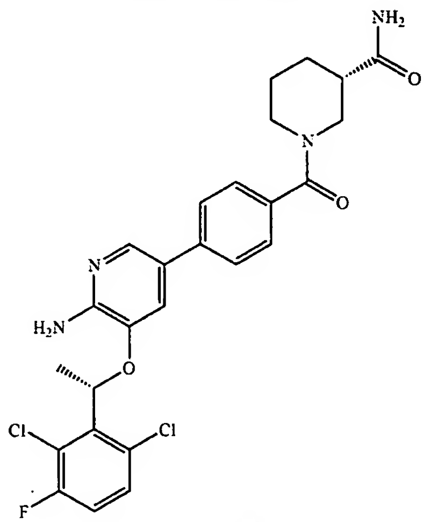


% inhibition = 76

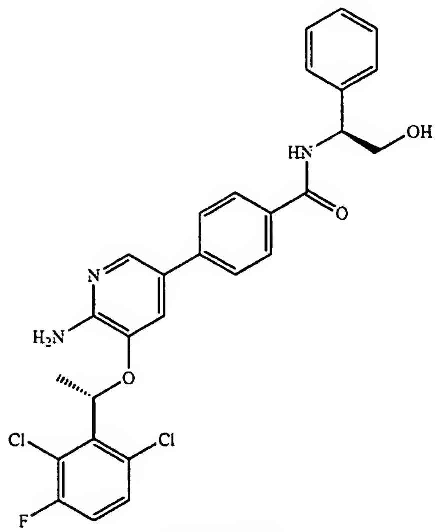


% inhibition = 66

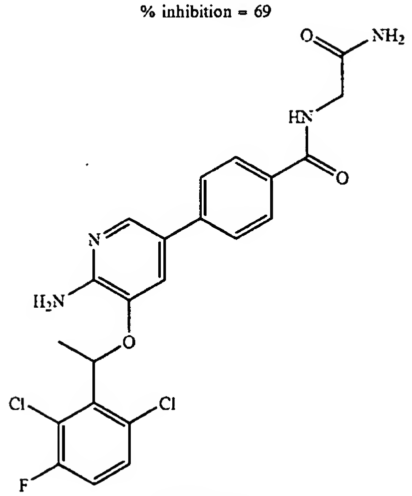
TABLE 5-continued



% inhibition = 84

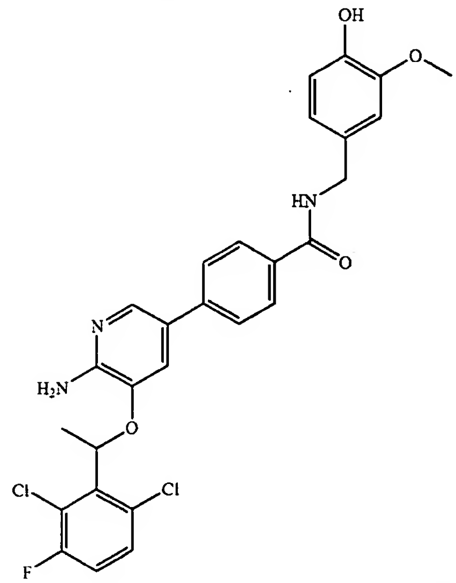


% inhibition = 69

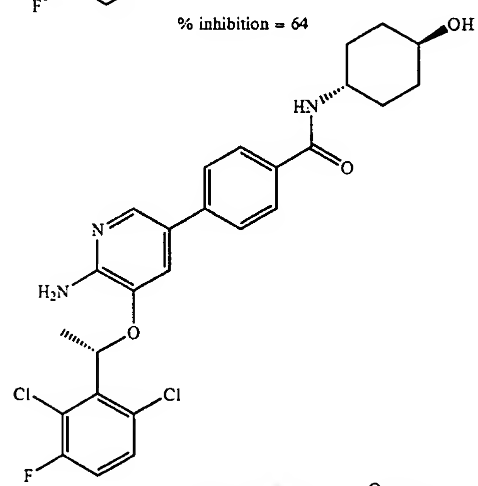


% inhibition = 86

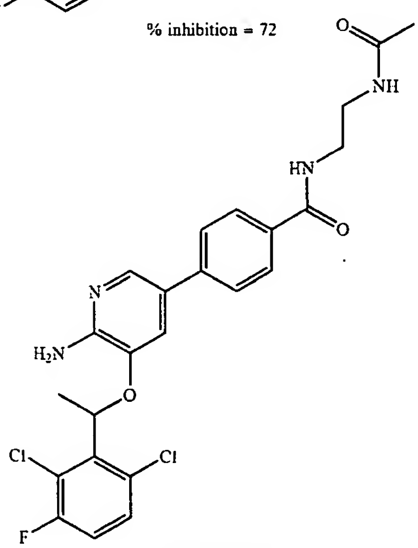
TABLE 5-continued



% inhibition = 64

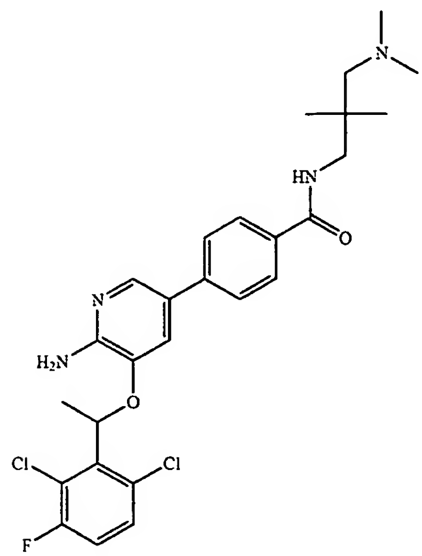


% inhibition = 72

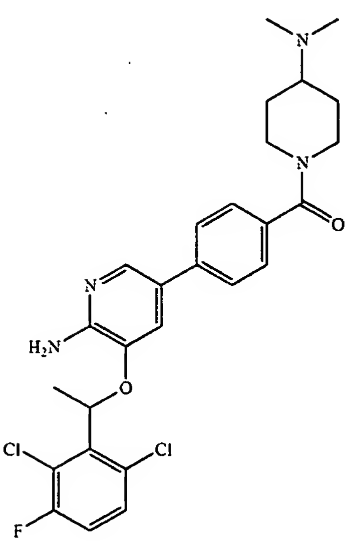


% inhibition = 71

TABLE 5-continued

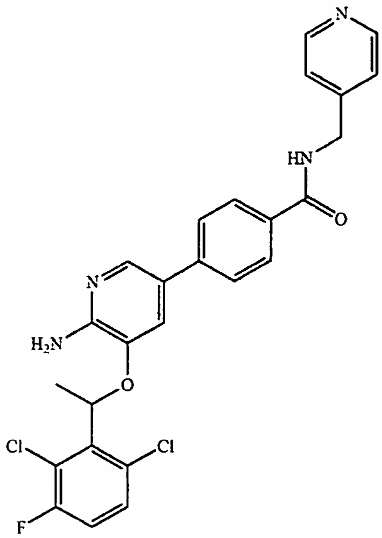


% inhibition = 77

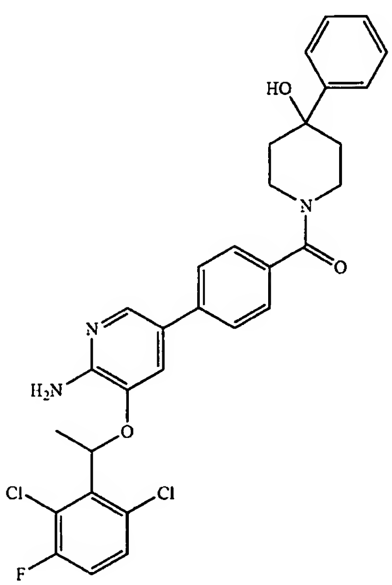


% inhibition = 92

TABLE 5-continued

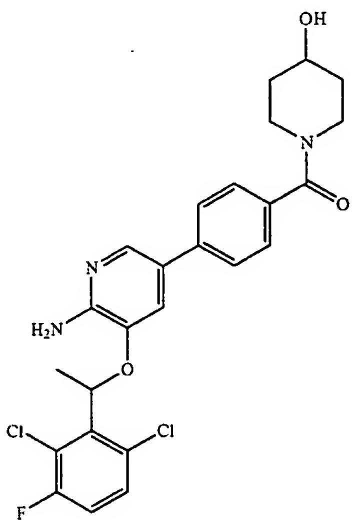


% inhibition = 74

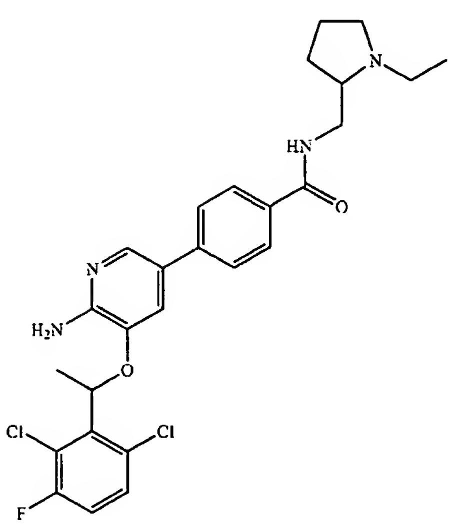


% inhibition = 64

TABLE 5-continued

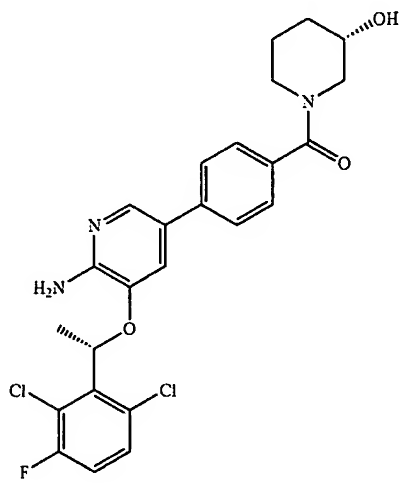


% inhibition = 86

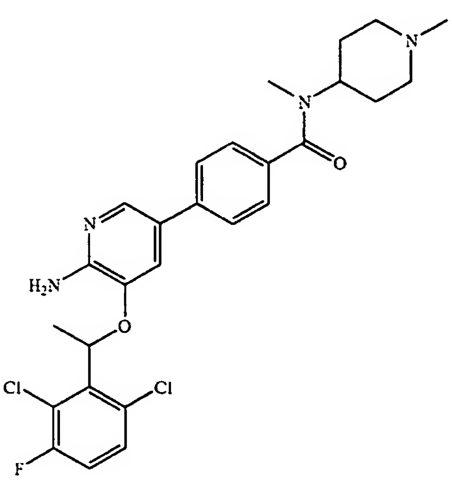


% inhibition = 80

TABLE 5-continued



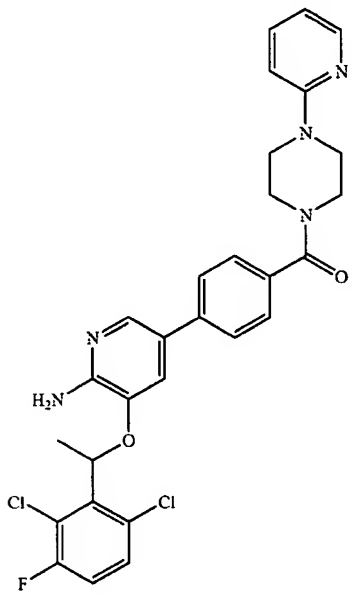
% inhibition = 85



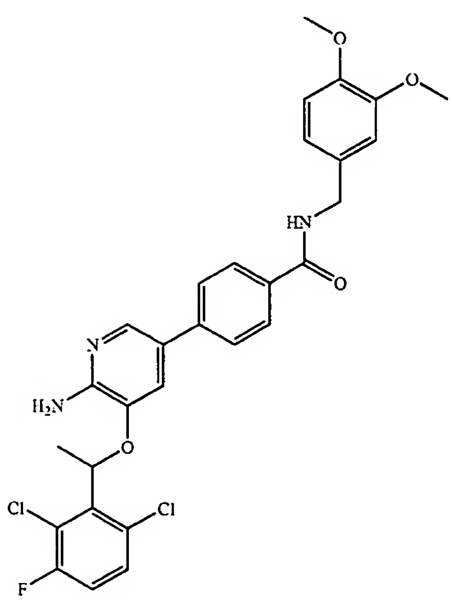
% inhibition = 92

TABLE 5-continued

Section C: Examples L-33 to L-48

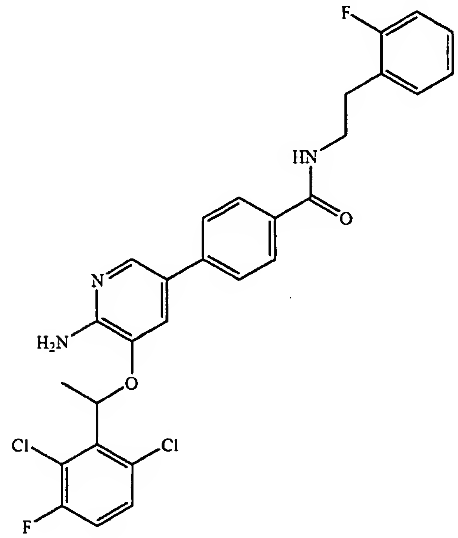


% inhibition = 63

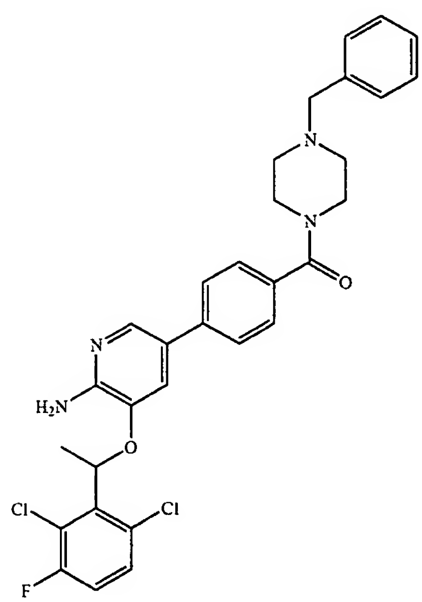


% inhibition = 62

TABLE 5-continued

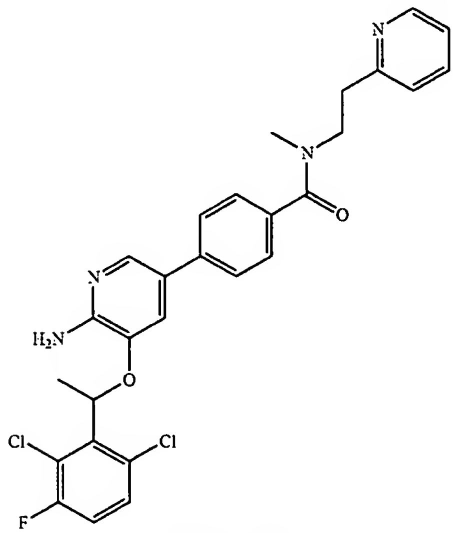


% inhibition = 55

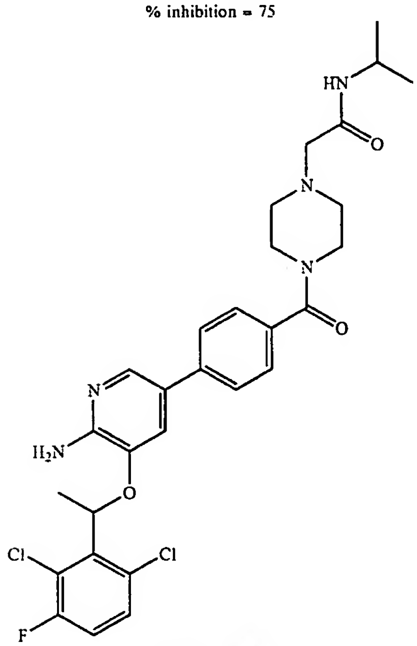


% inhibition = 62

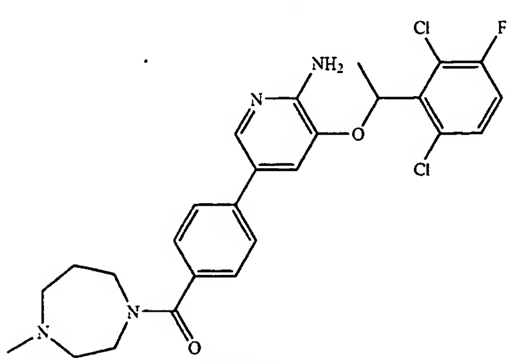
TABLE 5-continued



% inhibition = 75

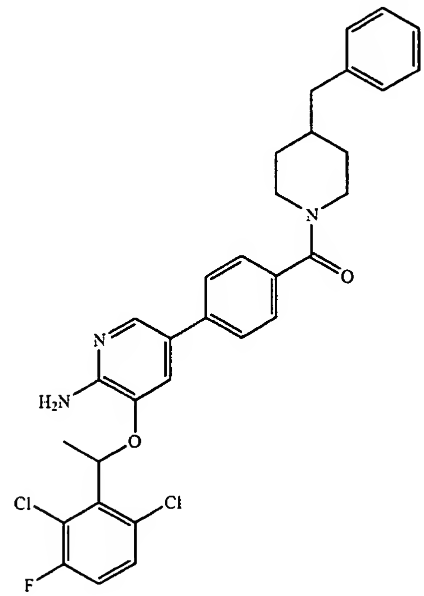


% inhibition = 86

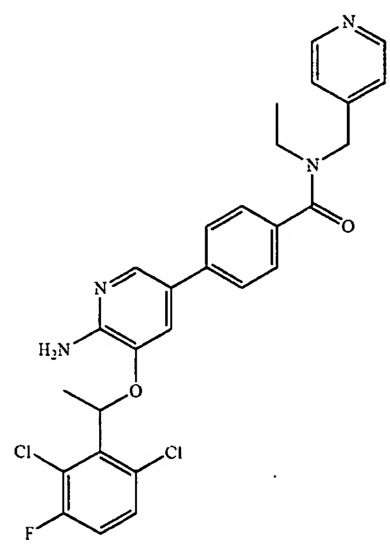


% inhibition = 77

TABLE 5-continued

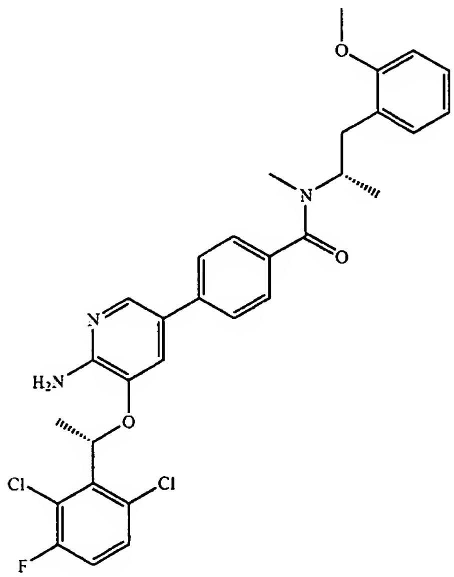


% inhibition = 55

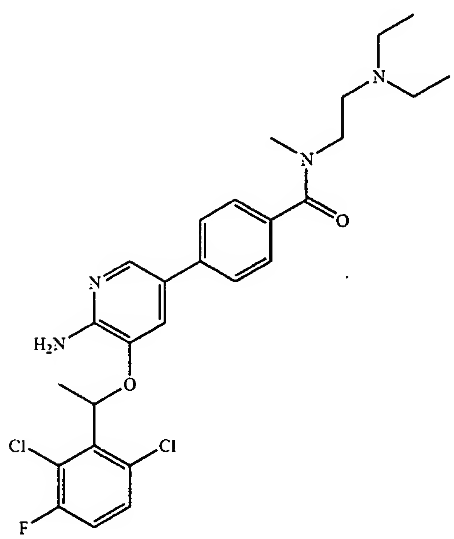


% inhibition = 84

TABLE 5-continued

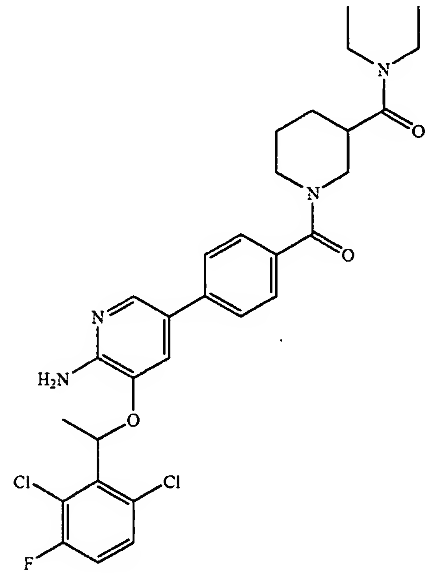


% inhibition = 55

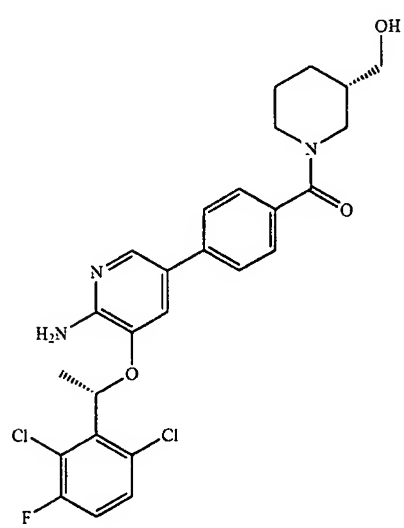


% inhibition = 85

TABLE 5-continued

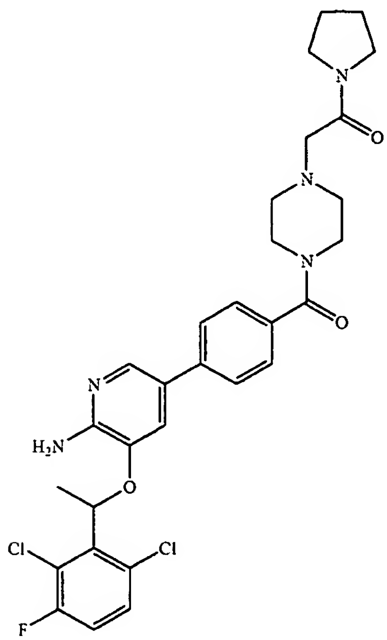


% inhibition = 55

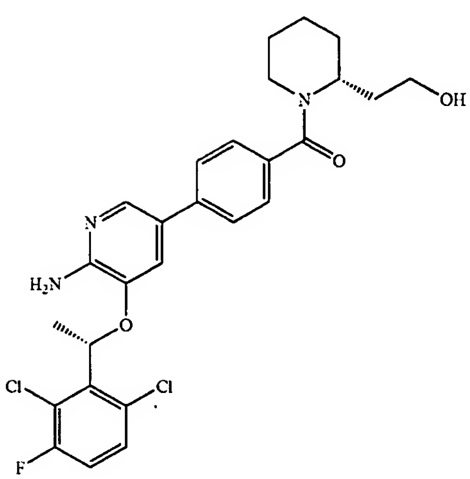


% inhibition = 84

TABLE 5-continued

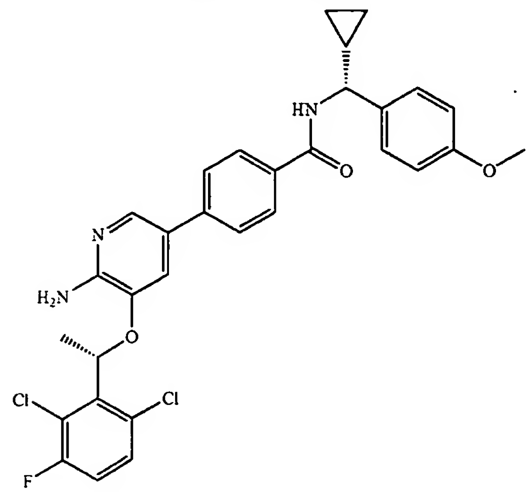


% inhibition = 78



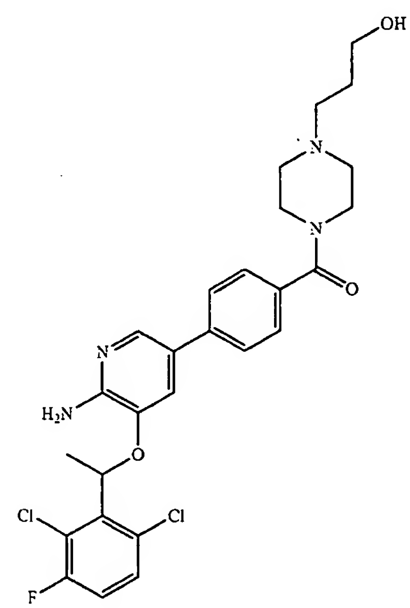
% inhibition = 83

TABLE 5-continued



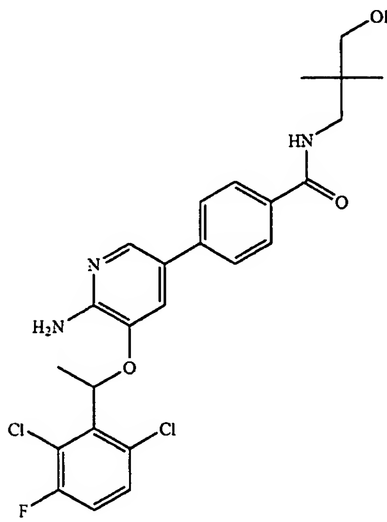
% inhibition = 67

Section D: Examples L-49 to L-64

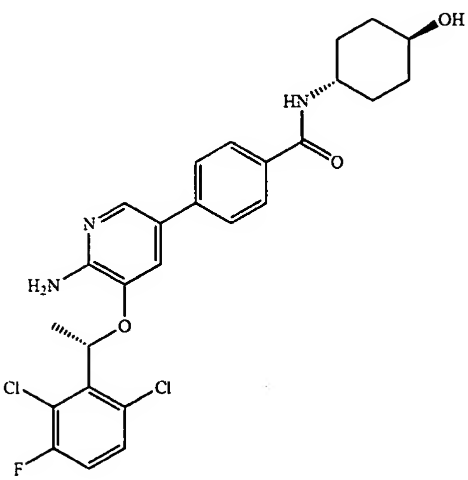


% inhibition = 74

TABLE 5-continued

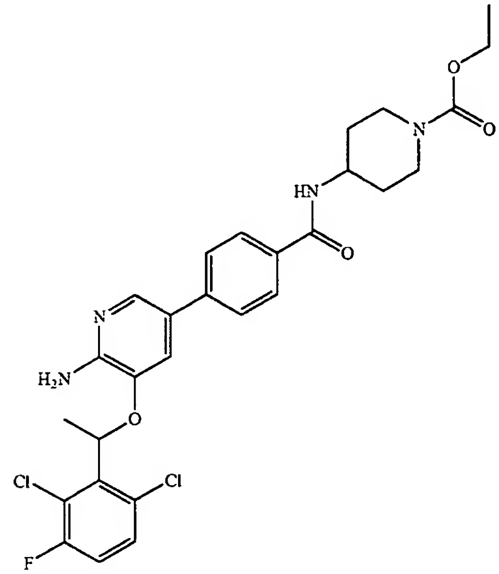


% inhibition = 73

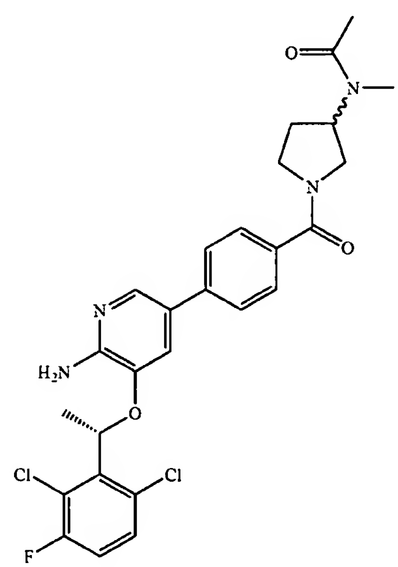


% inhibition = 73

TABLE 5-continued

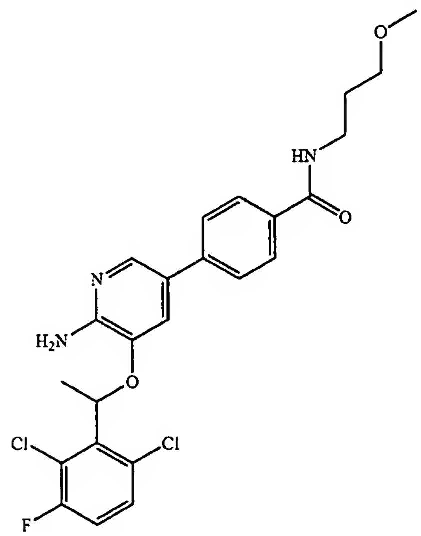


% inhibition = 66

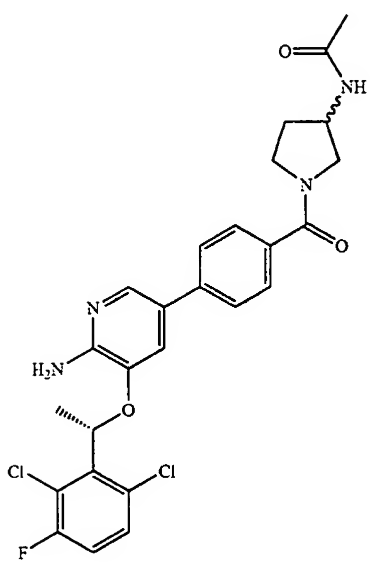


% inhibition = 70

TABLE 5-continued

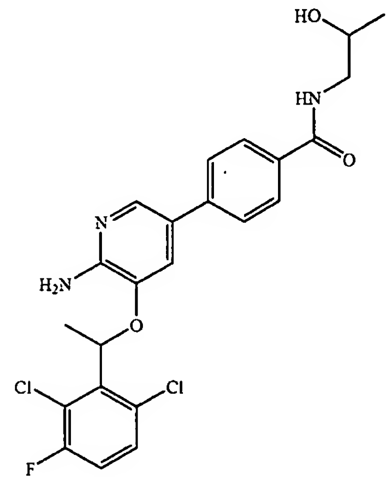


% inhibition = 95

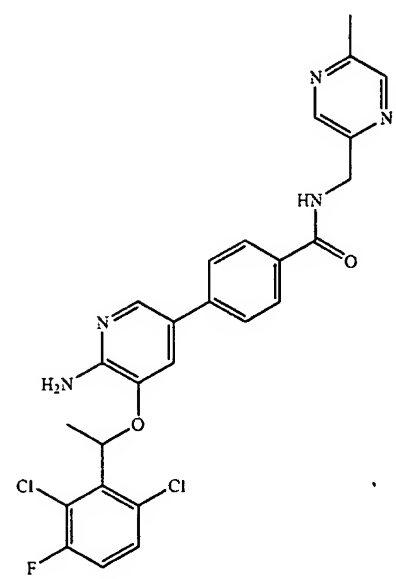


% inhibition = 77

TABLE 5-continued

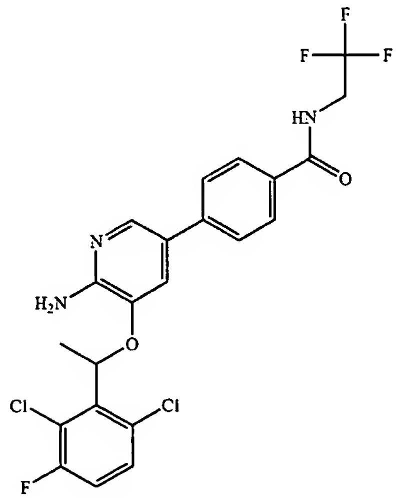


% inhibition = 83

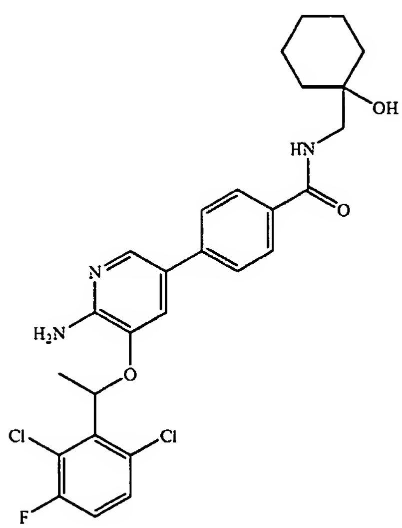


% inhibition = 76

TABLE 5-continued

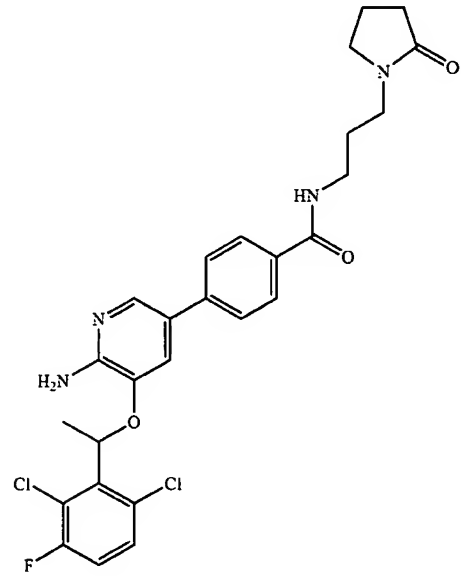


% inhibition = 78

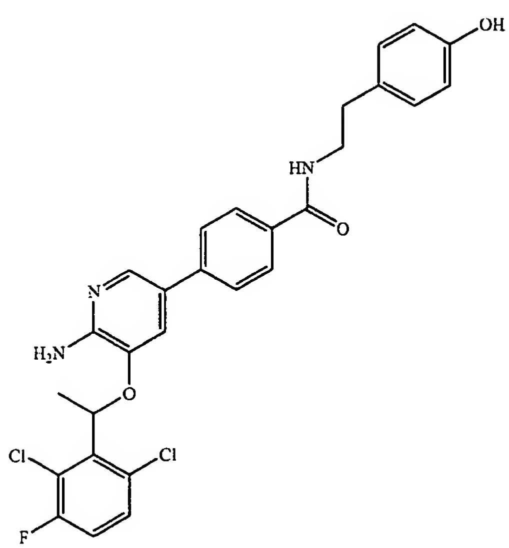


% inhibition = 81

TABLE 5-continued

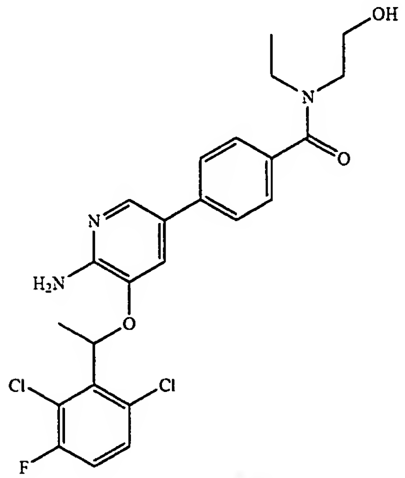


% inhibition = 83

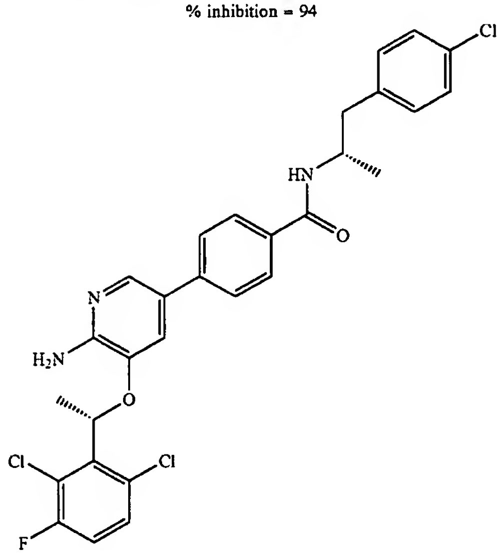


% inhibition = 71

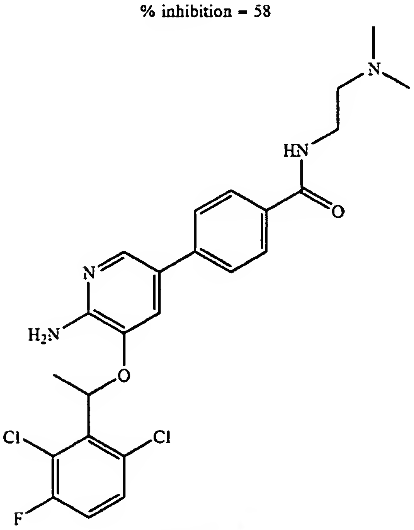
TABLE 5-continued



% inhibition = 94



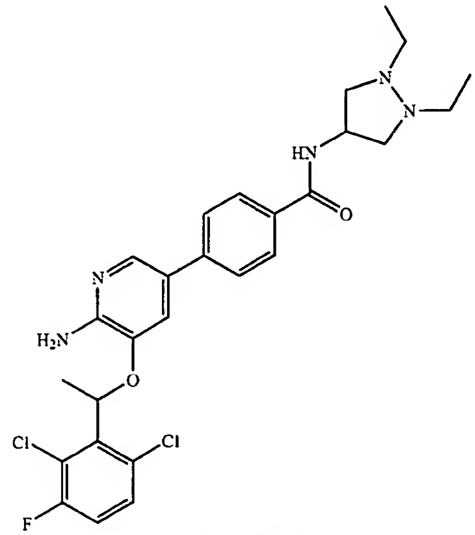
% inhibition = 58



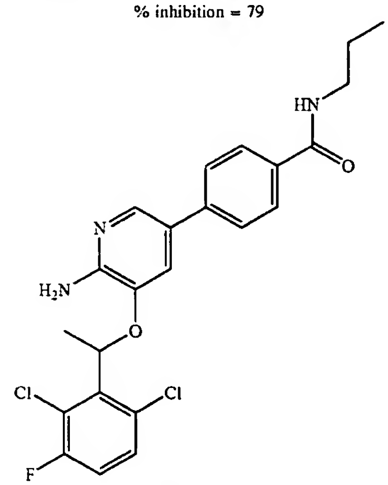
% inhibition = 85

TABLE 5-continued

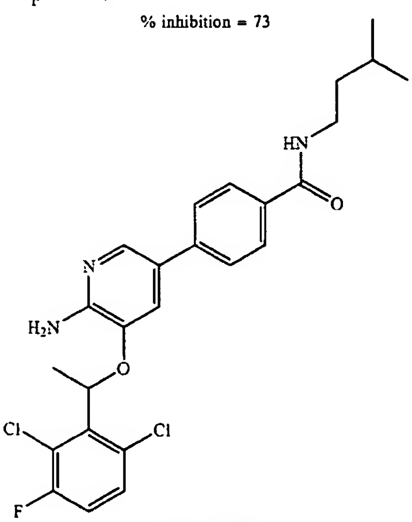
Section E: Examples L-65 to L-80



% inhibition = 79

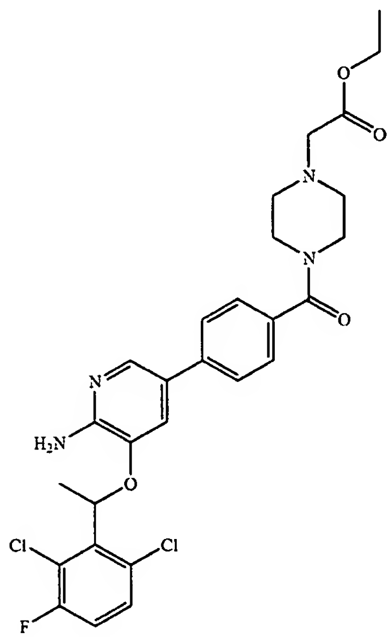


% inhibition = 73

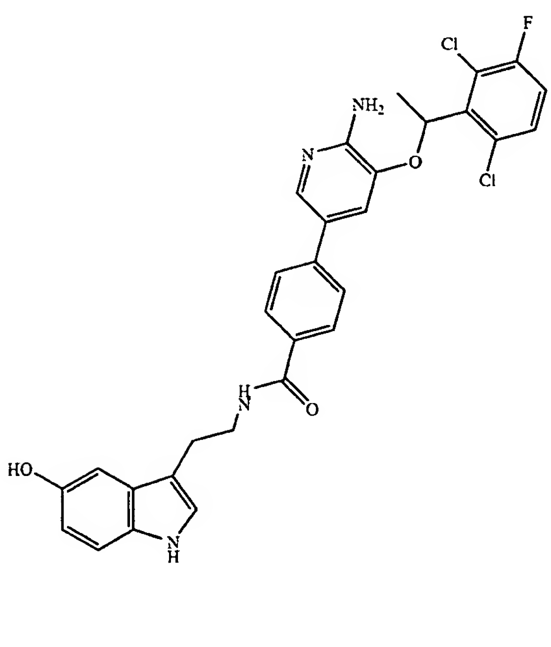


% inhibition = 53

TABLE 5-continued

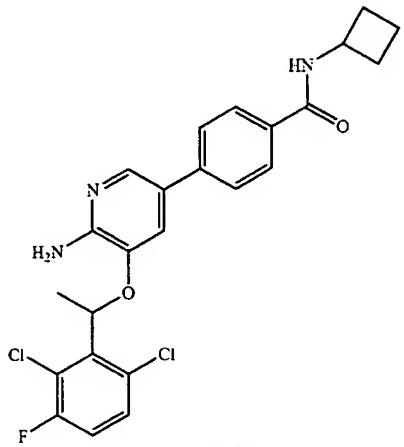


% inhibition = 70

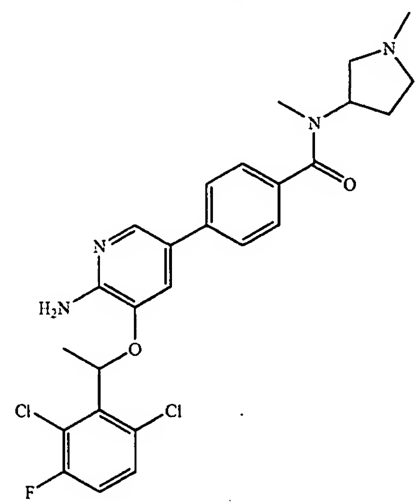


% inhibition = 66

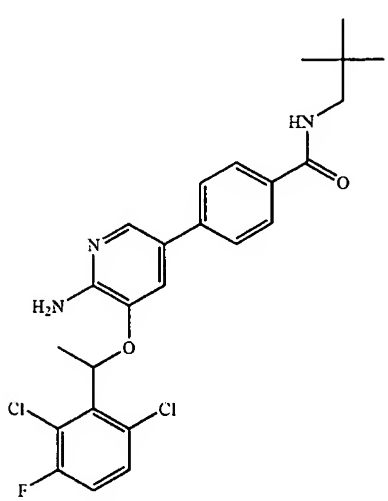
TABLE 5-continued



% inhibition = 71

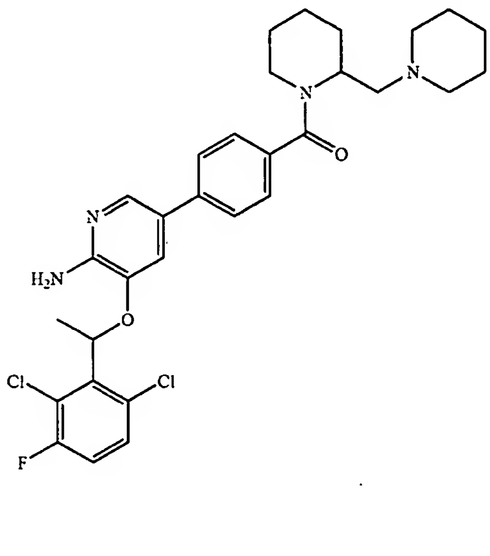


% inhibition = 92

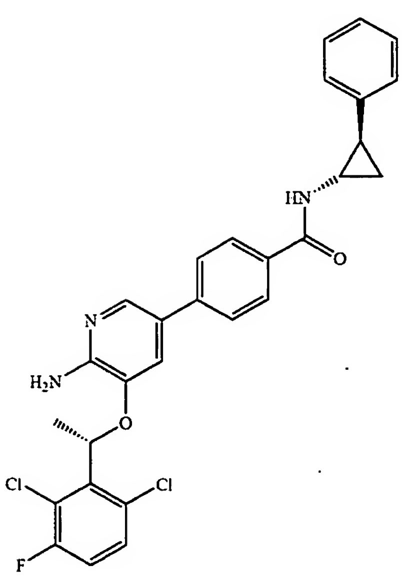


% inhibition = 62

TABLE 5-continued

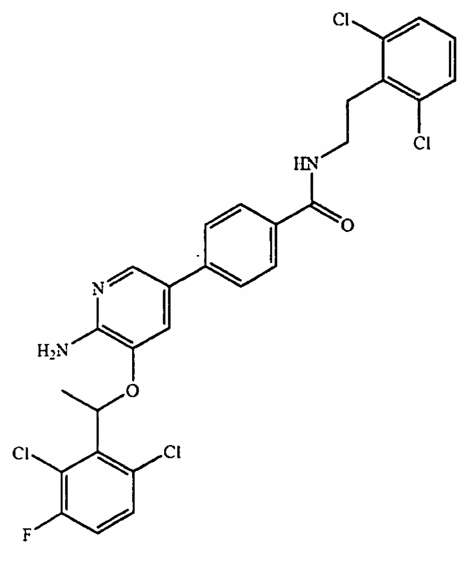


% inhibition = 90

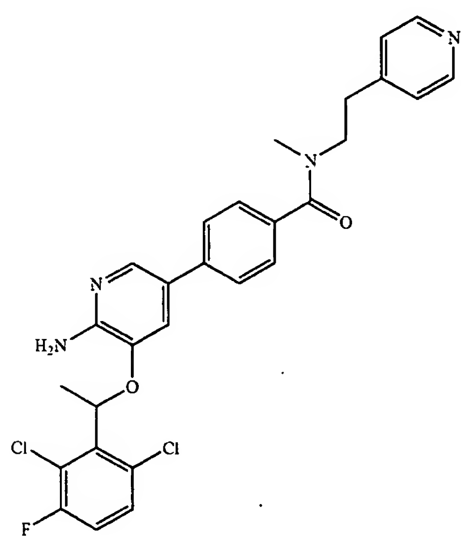


% inhibition = 65

TABLE 5-continued

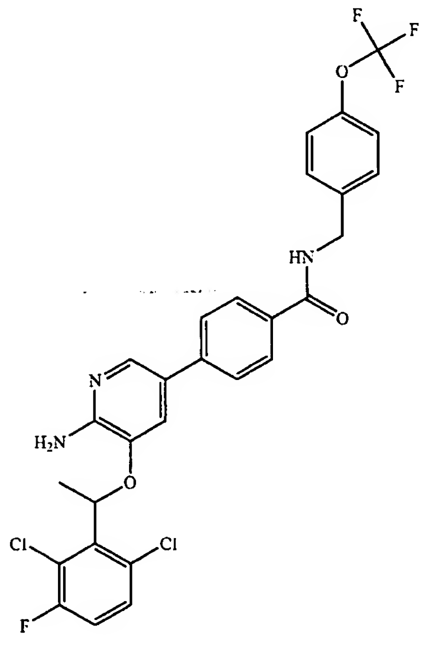


% inhibition = 53

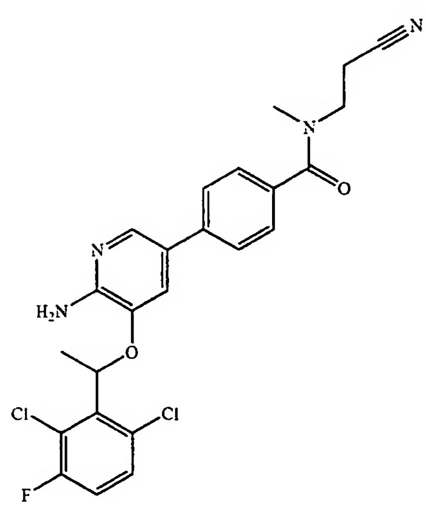


% inhibition = 73

TABLE 5-continued

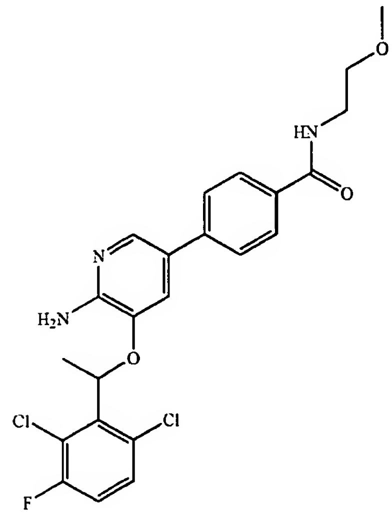


% inhibition = 54

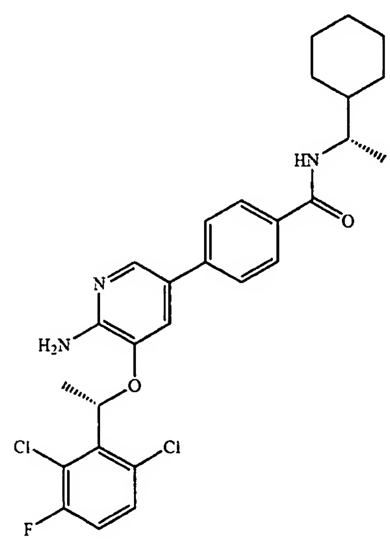


% inhibition = 68

TABLE 5-continued



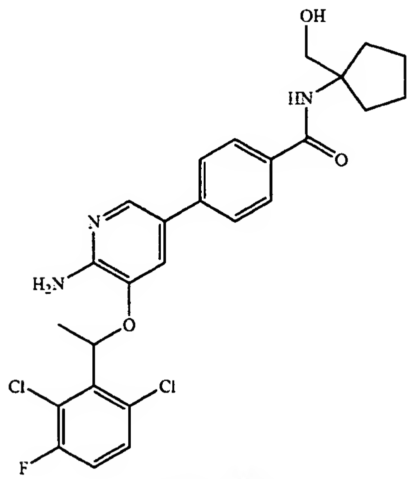
% inhibition = 73



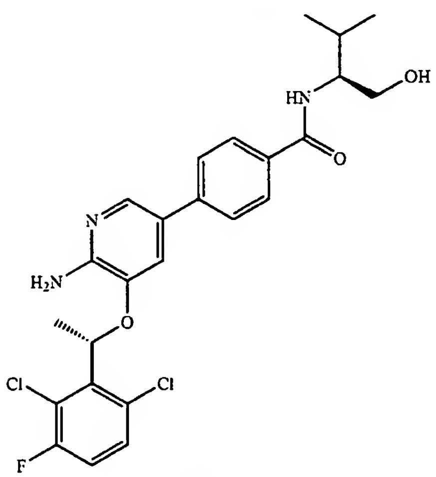
% inhibition = 60

TABLE 5-continued

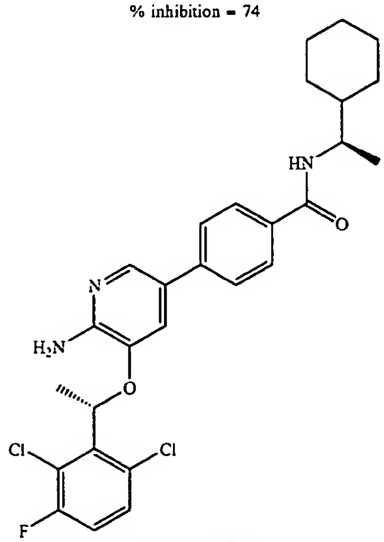
Section F: Examples L-81 to L-96



% inhibition = 67

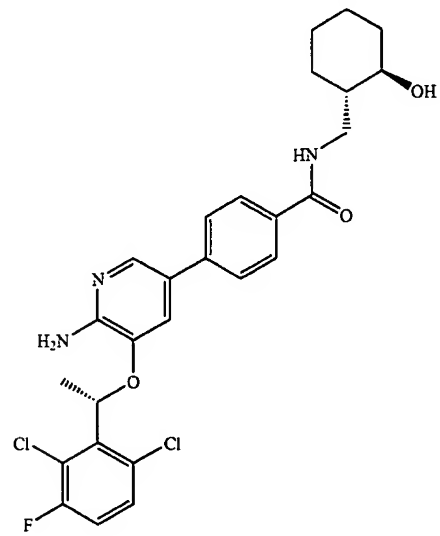


% inhibition = 74

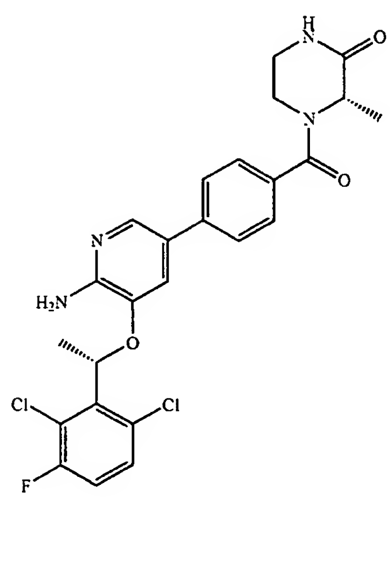


% inhibition = 54

TABLE 5-continued

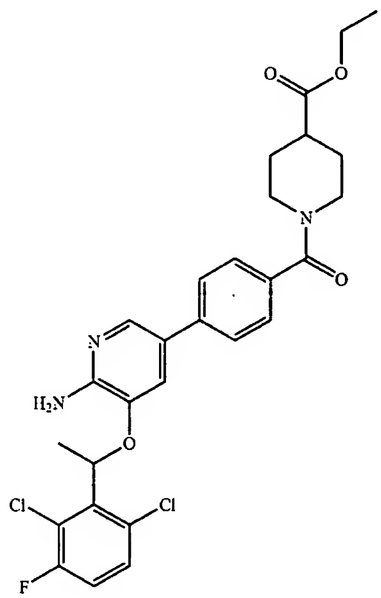


% inhibition = 67

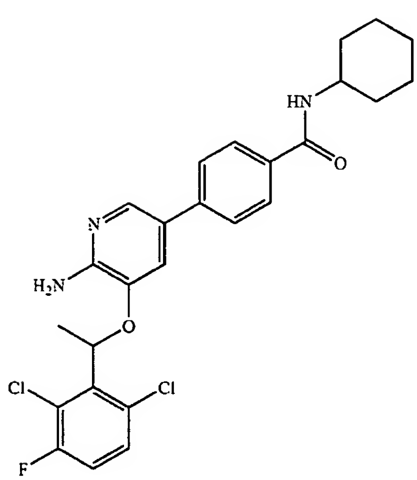


% inhibition = 86

TABLE 5-continued

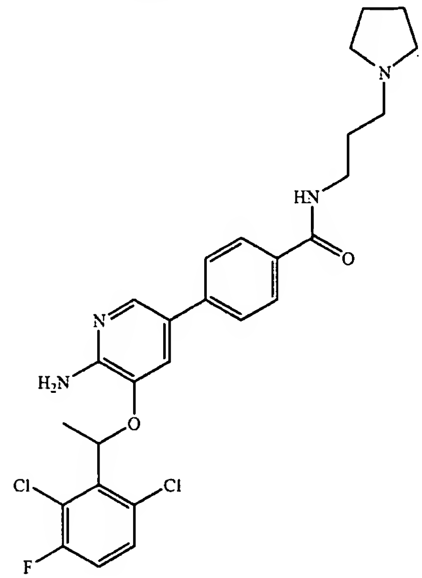


% inhibition = 57

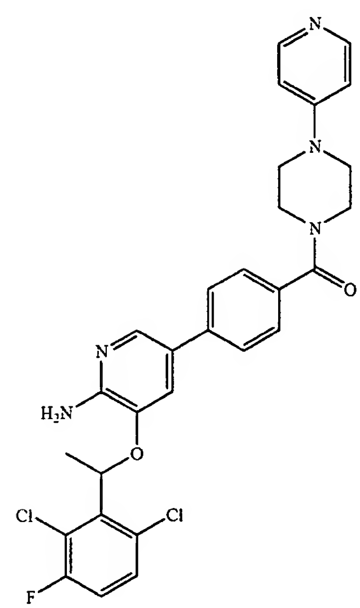


% inhibition = 56

TABLE 5-continued

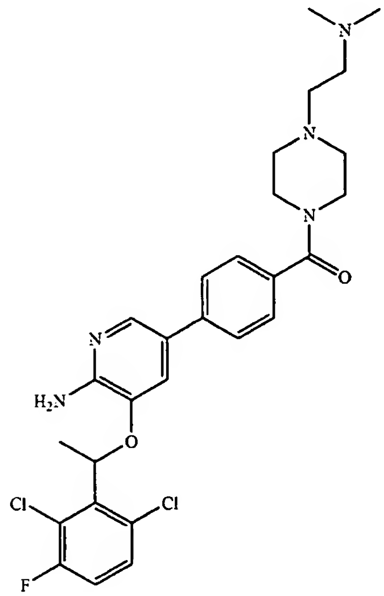


% inhibition = 90

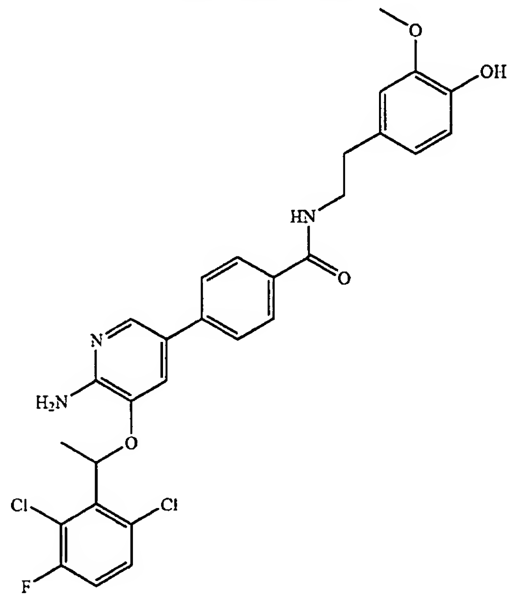


% inhibition = 96

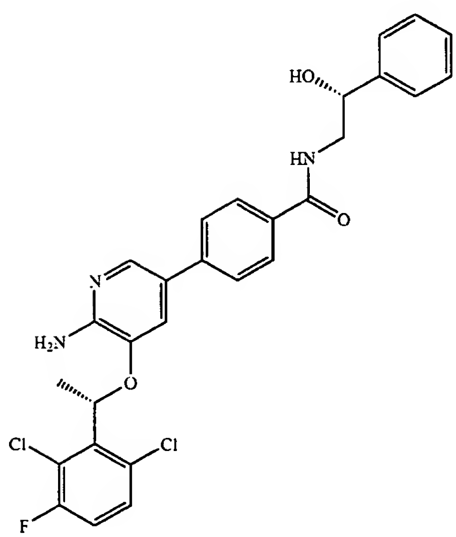
TABLE 5-continued



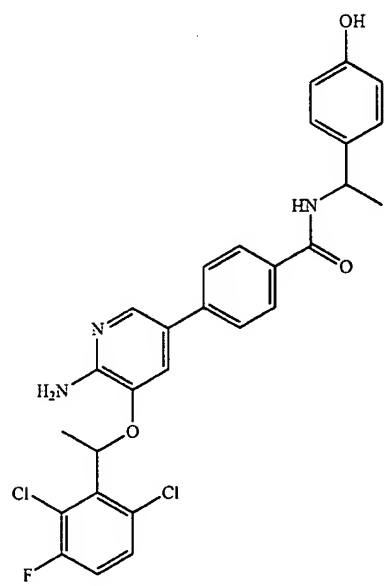
% inhibition = 85



% inhibition = 64

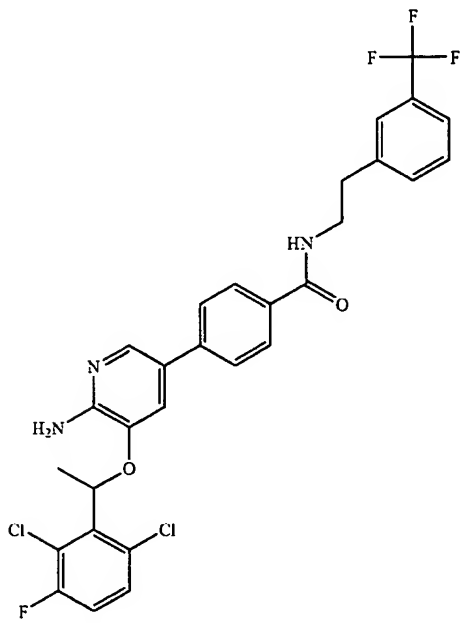


% inhibition = 69

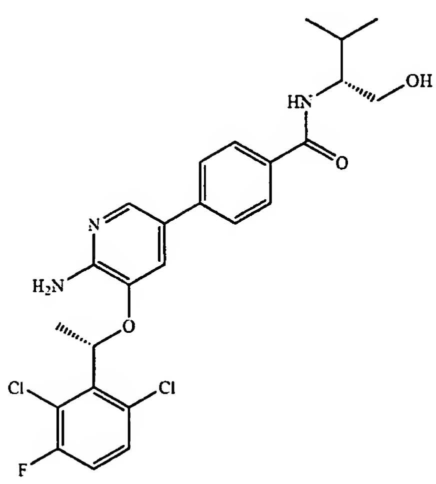


% inhibition = 62

TABLE 5-continued

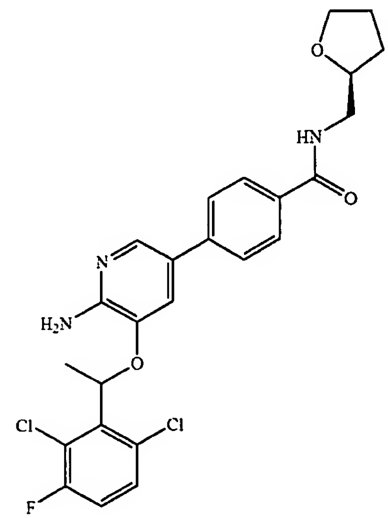


% inhibition = 51



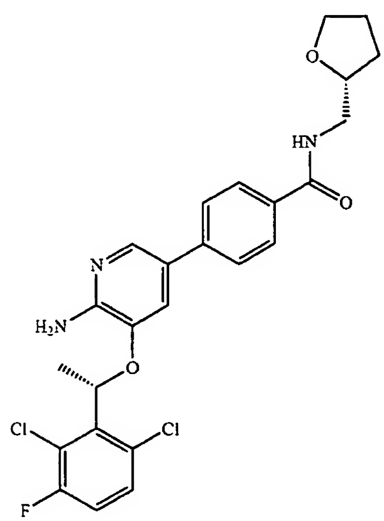
% inhibition = 65

TABLE 5-continued



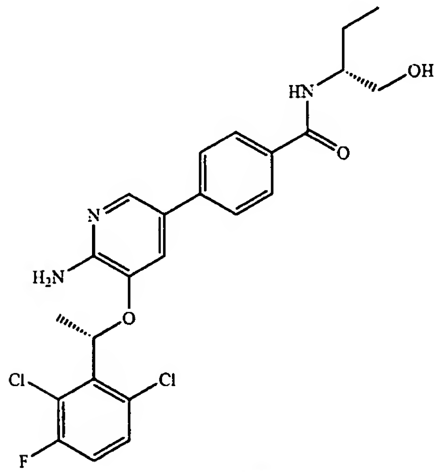
% inhibition = 61

Section G: Examples L-97 to L-112

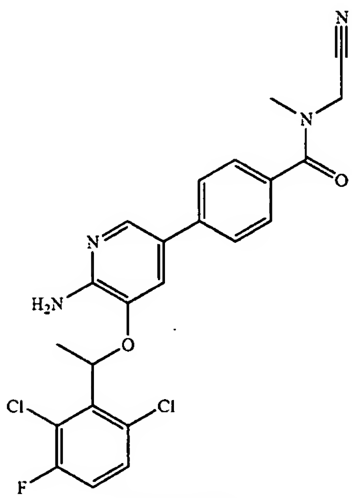


% inhibition = 60

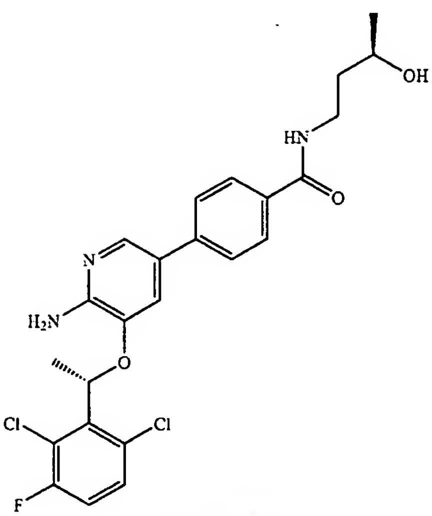
TABLE 5-continued



% inhibition = 73

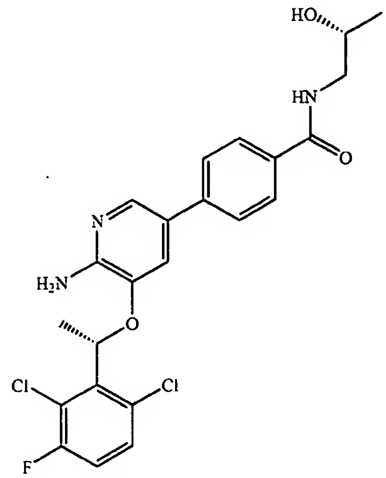


% inhibition = 83

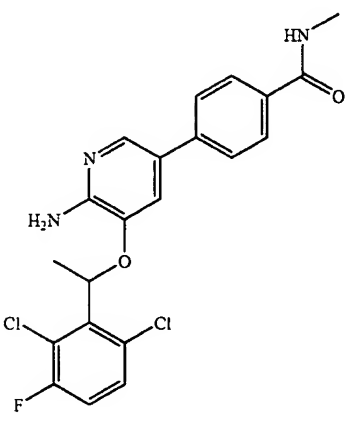


% inhibition = 77

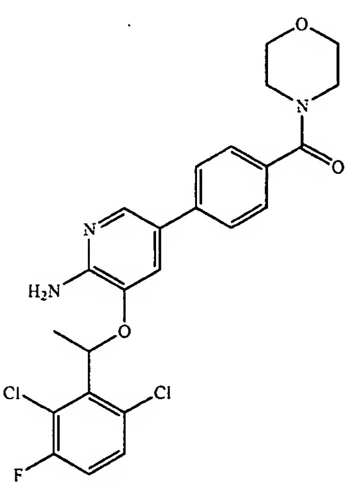
TABLE 5-continued



% inhibition = 79

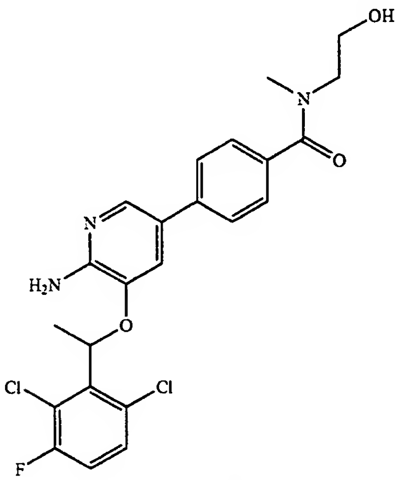


% inhibition = 82

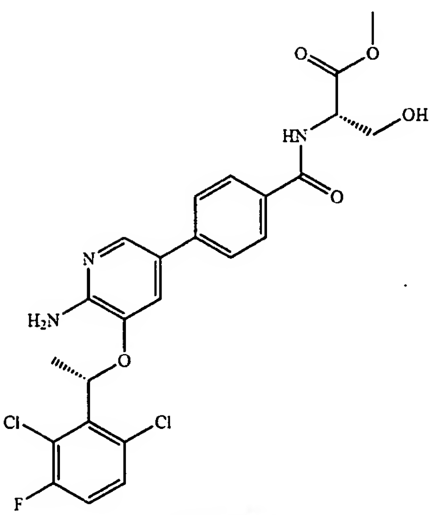


% inhibition = 91

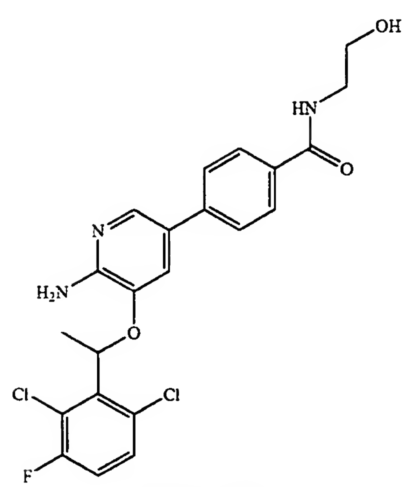
TABLE 5-continued



% inhibition = 89

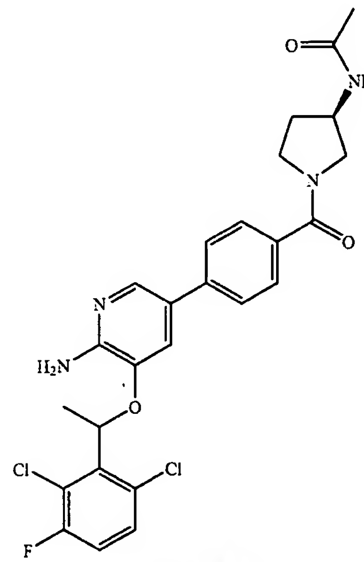


% inhibition = 81

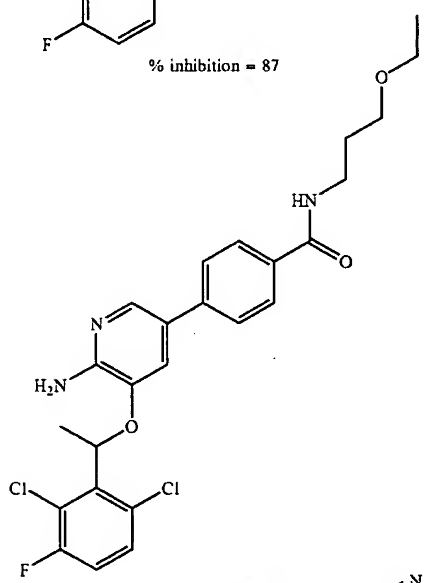


% inhibition = 89

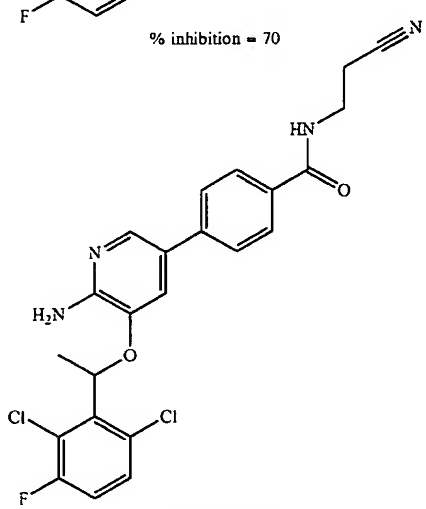
TABLE 5-continued



% inhibition = 87

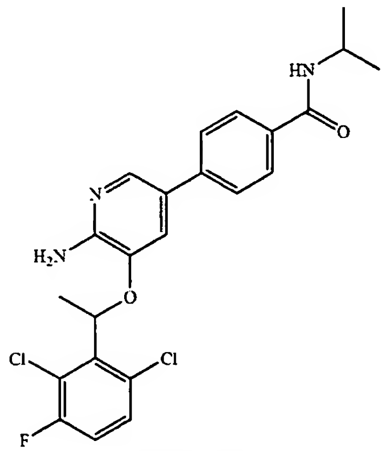


% inhibition = 70

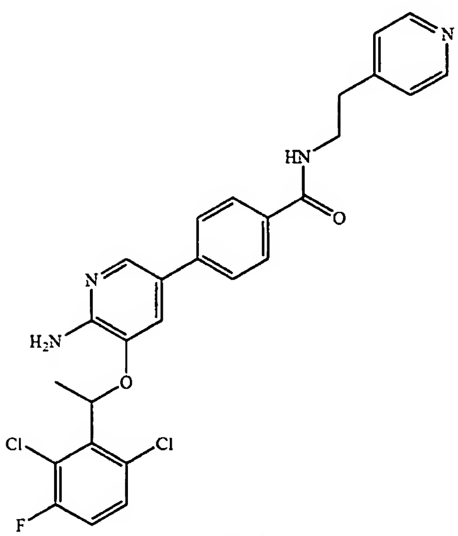


% inhibition = 76

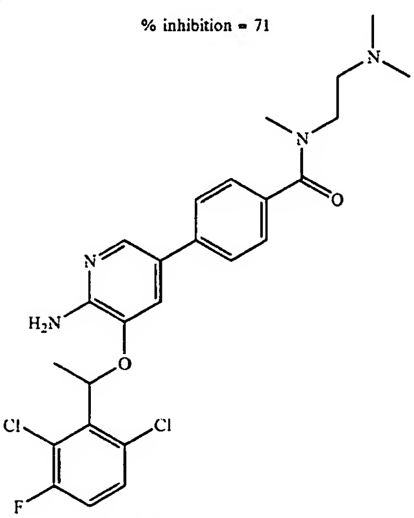
TABLE 5-continued



% inhibition = 71



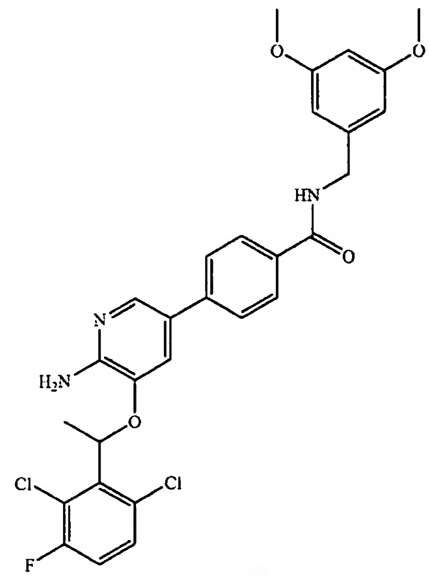
% inhibition = 71



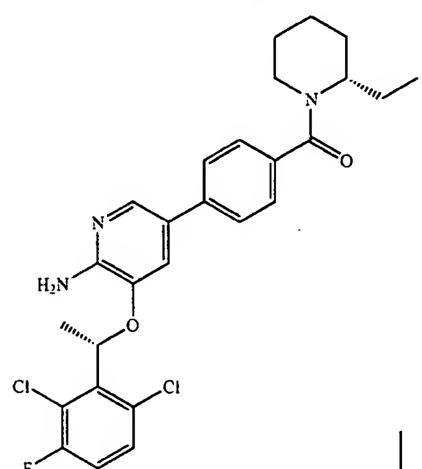
% inhibition = 85

TABLE 5-continued

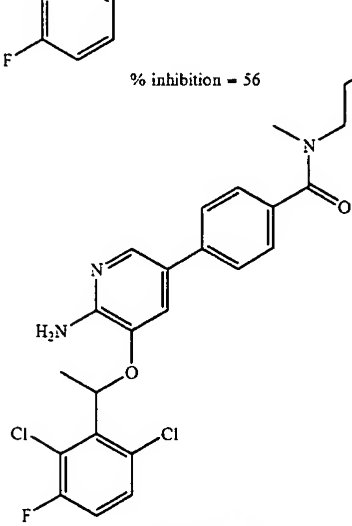
Section H: Examples L-113 to L-128



% inhibition = 57

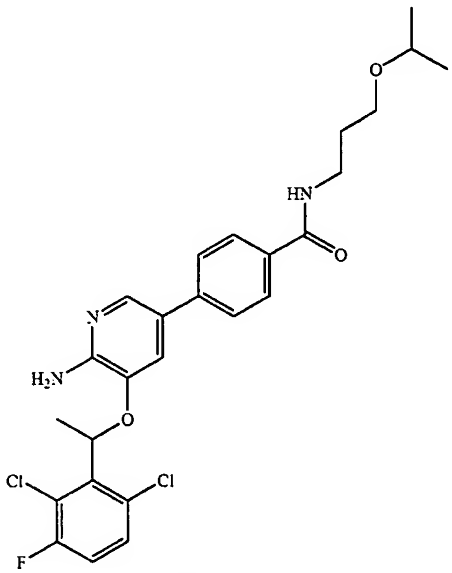


% inhibition = 56

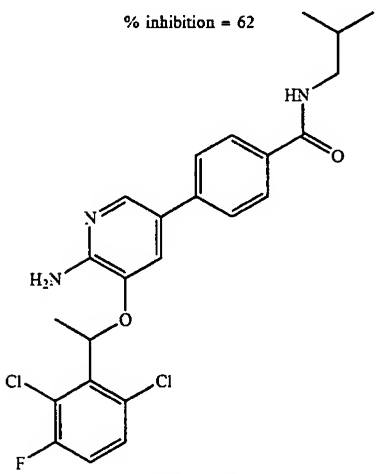


% inhibition = 63

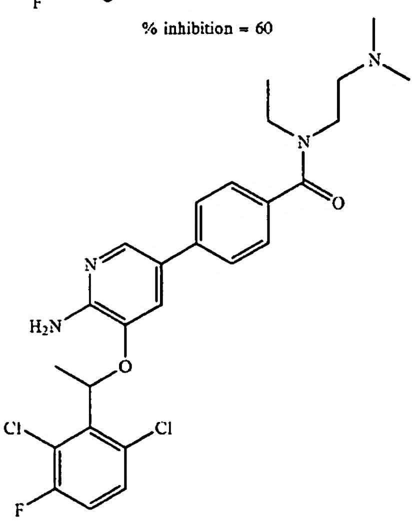
TABLE 5-continued



% inhibition = 62

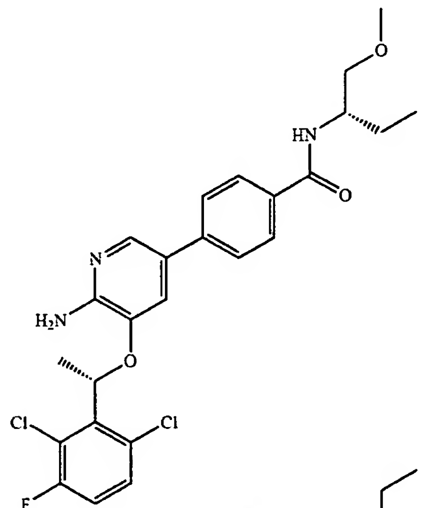


% inhibition = 60

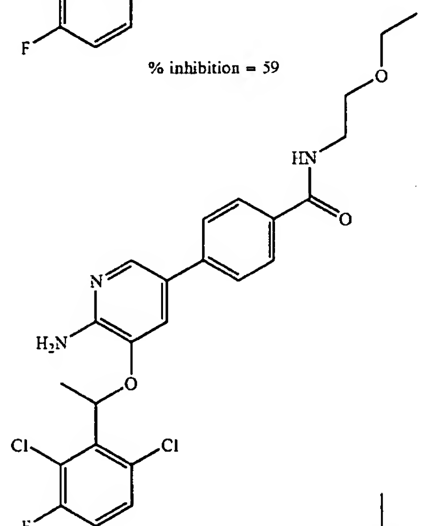


% inhibition = 86

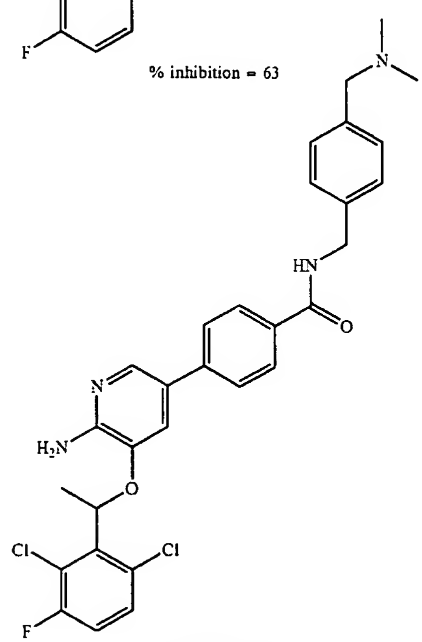
TABLE 5-continued



% inhibition = 59

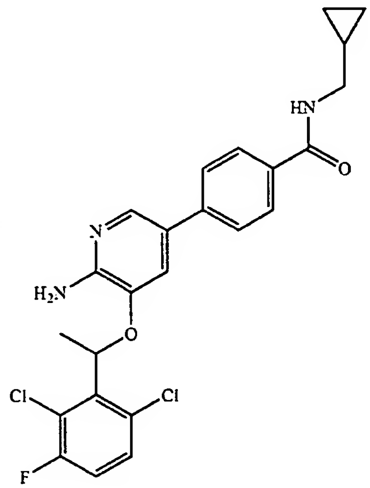


% inhibition = 63

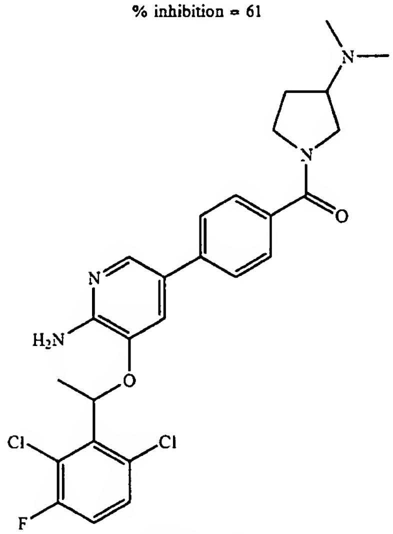


% inhibition = 75

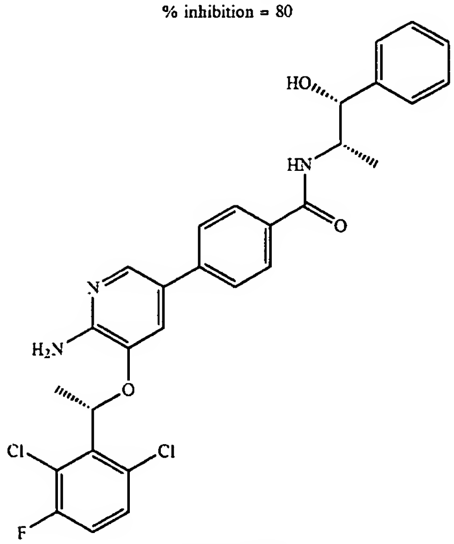
TABLE 5-continued



% inhibition = 61

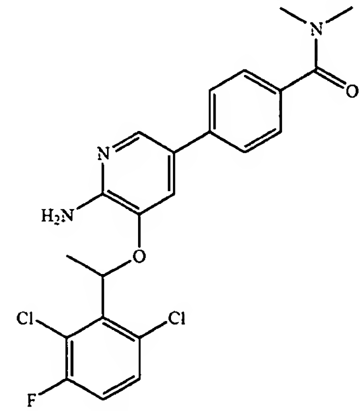


% inhibition = 80

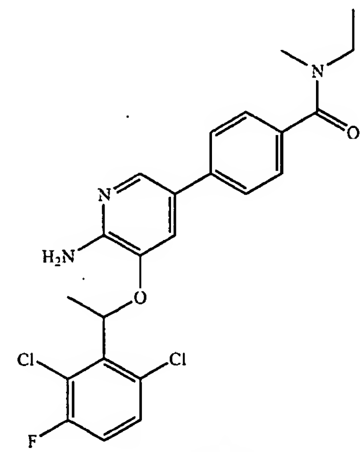


% inhibition = 69

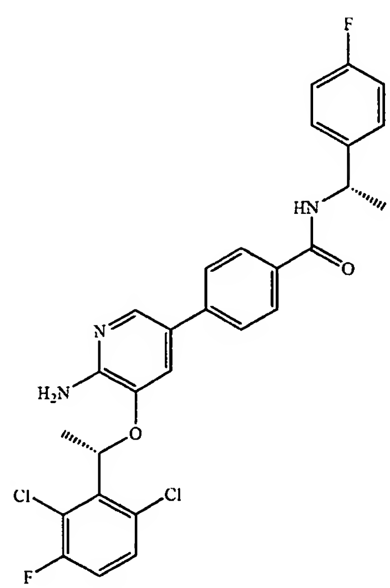
TABLE 5-continued



% inhibition = 77

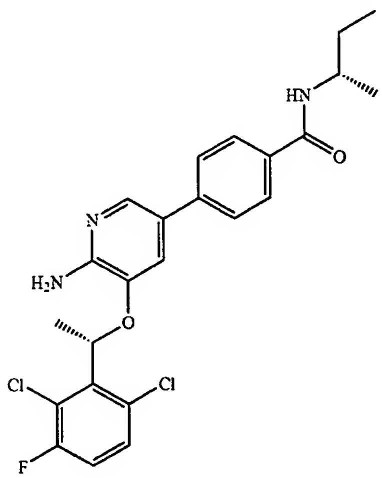


% inhibition = 52



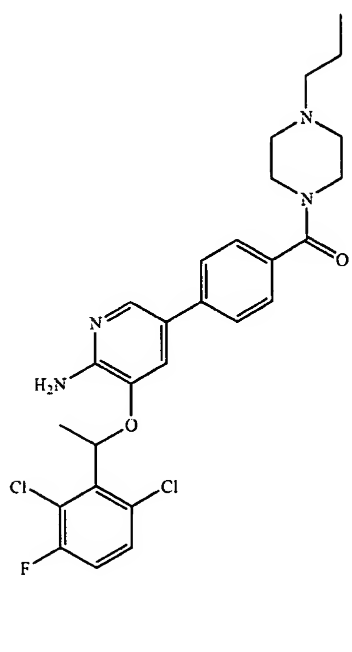
% inhibition = 56

TABLE 5-continued



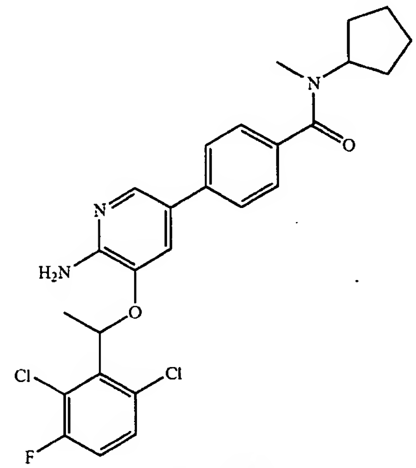
% inhibition = 64

Section I: Examples L-129 to L-144

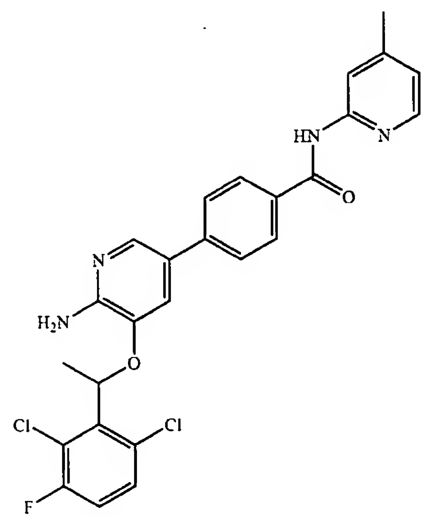


% inhibition = 82

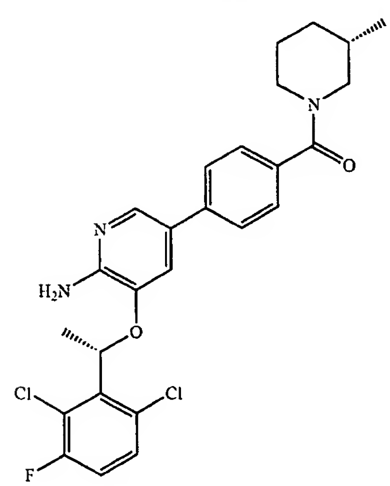
TABLE 5-continued



% inhibition = 60

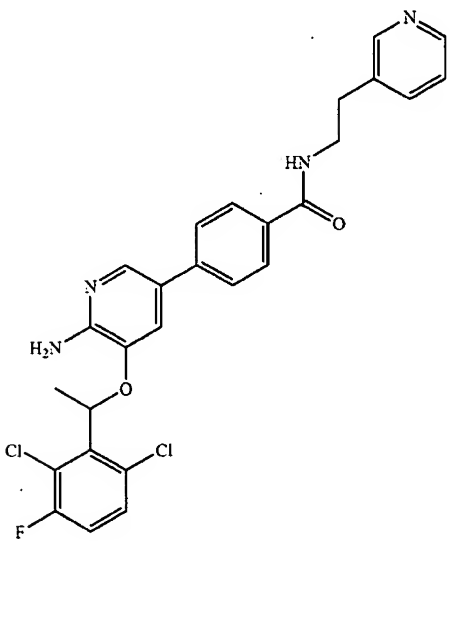


% inhibition = 61

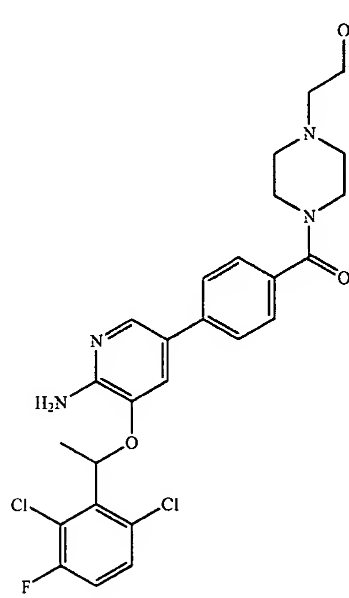


% inhibition = 65

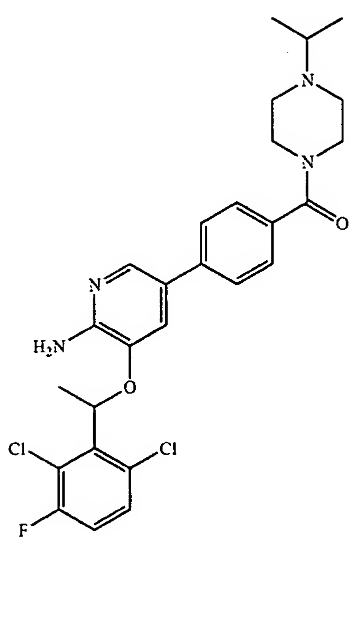
TABLE 5-continued



% inhibition = 68

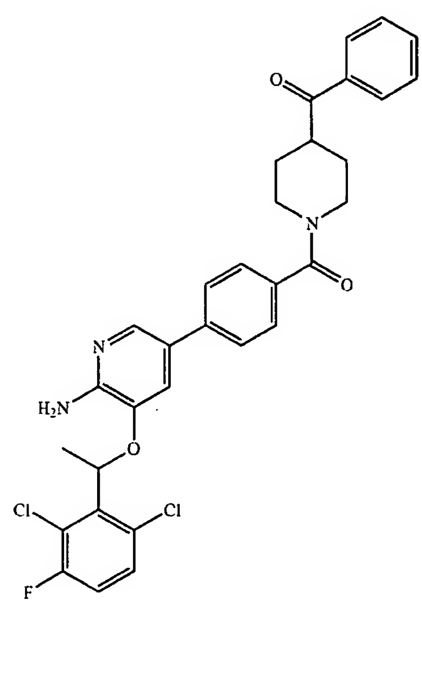


% inhibition = 76



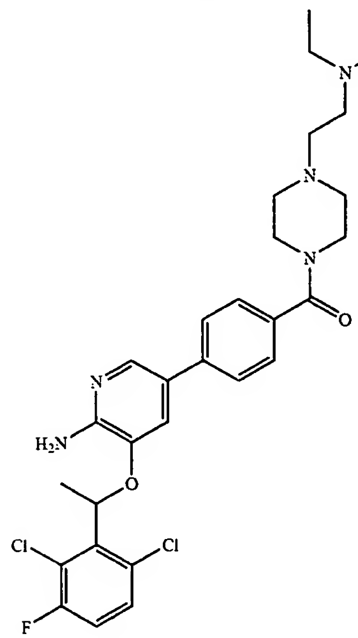
% inhibition = 76

TABLE 5-continued

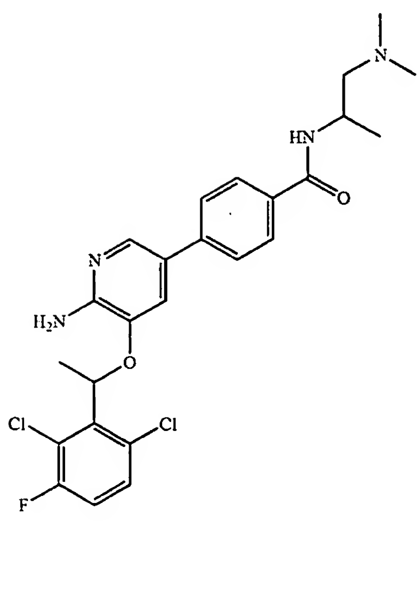


% inhibition = 61

TABLE 5-continued

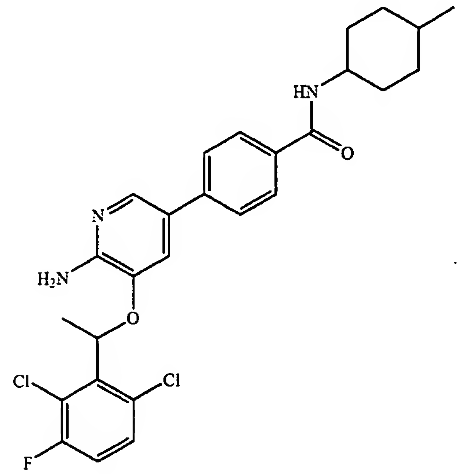


% inhibition = 78

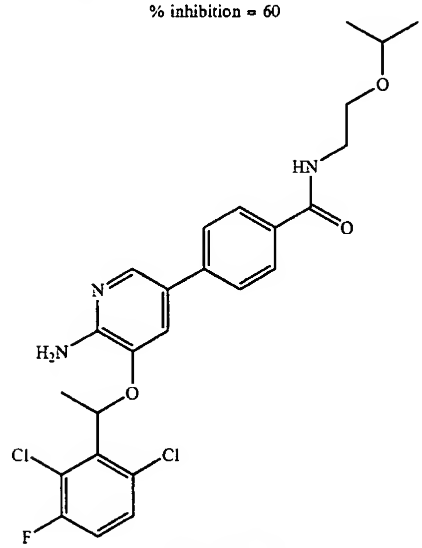


% inhibition = 83

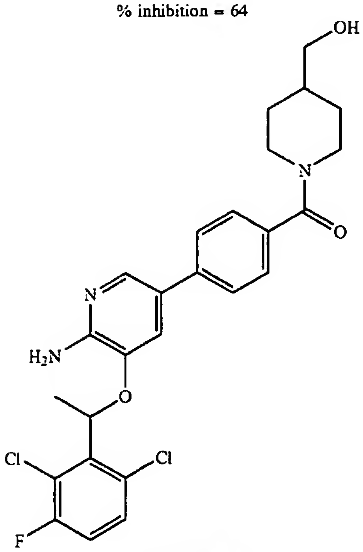
TABLE 5-continued



% inhibition = 60

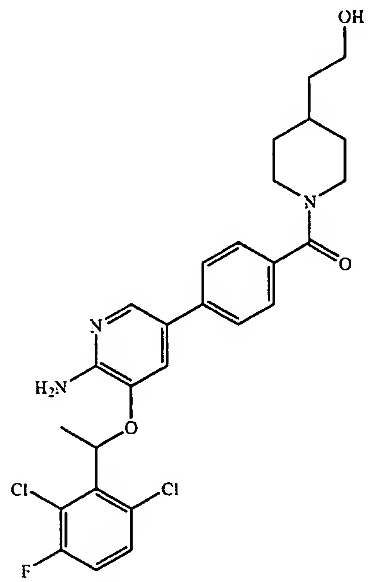


% inhibition = 64

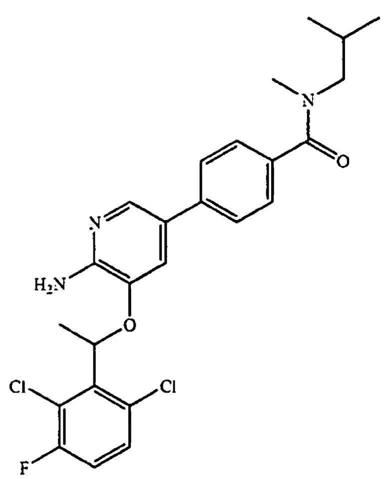


% inhibition = 79

TABLE 5-continued

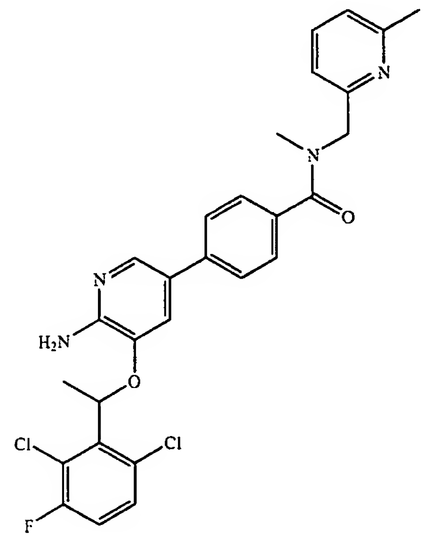


% inhibition = 72



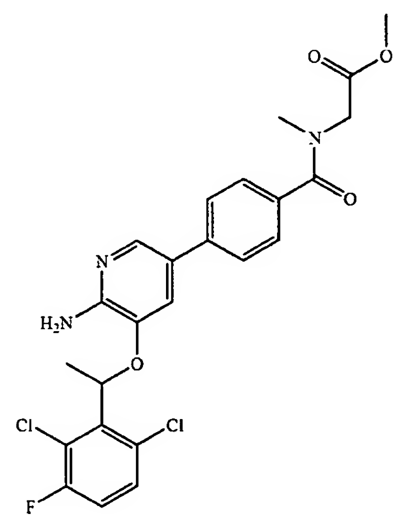
% inhibition = 59

TABLE 5-continued



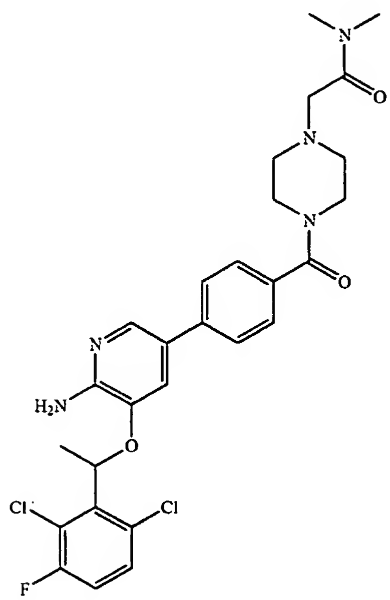
% inhibition = 71

Section J: Examples L-145 to L-160

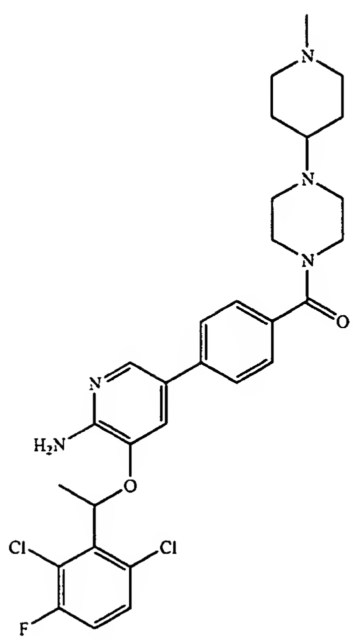


% inhibition = 77

TABLE 5-continued

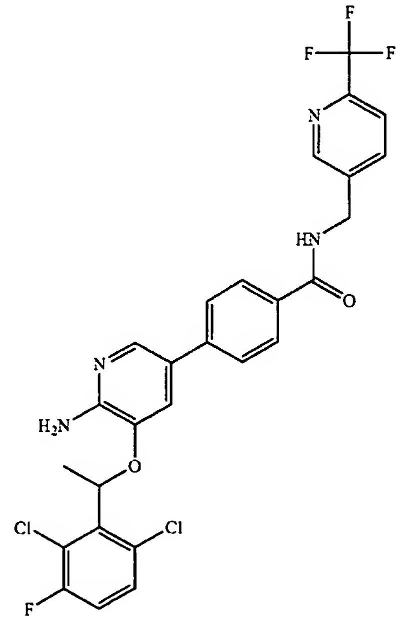


% inhibition = 89

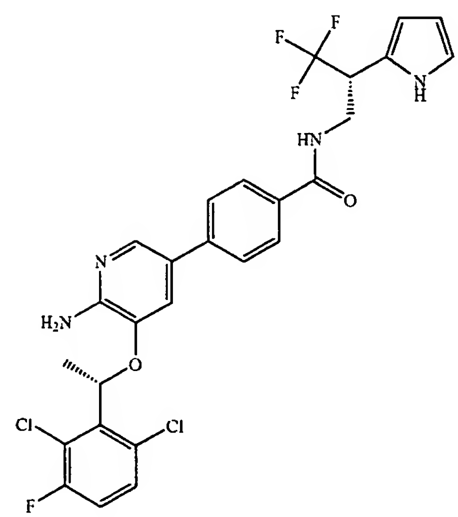


% inhibition = 96

TABLE 5-continued

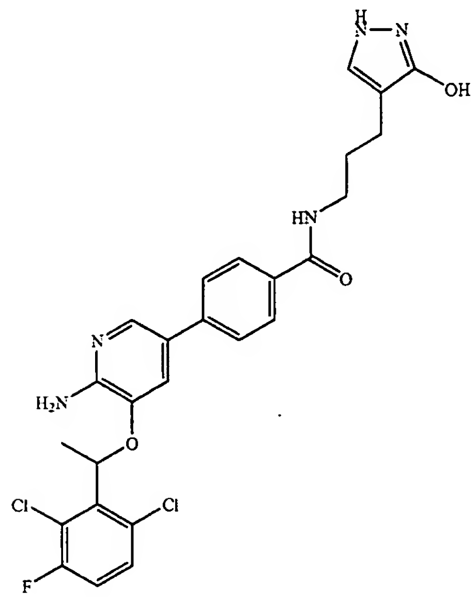


% inhibition = 62

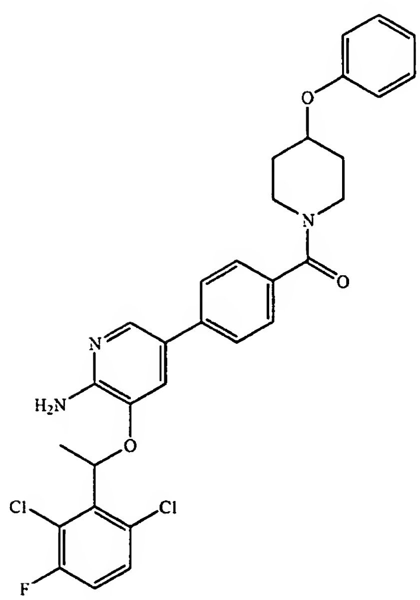


% inhibition = 70

TABLE 5-continued

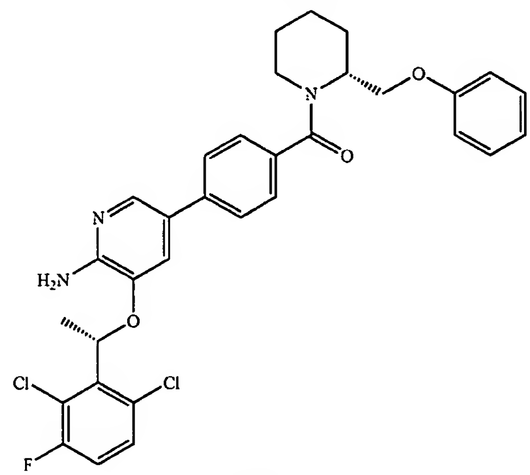


% inhibition = 81

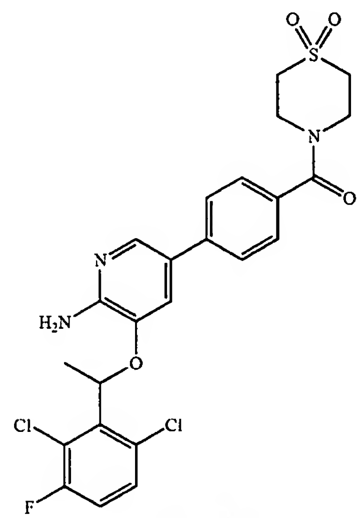


% inhibition = 58

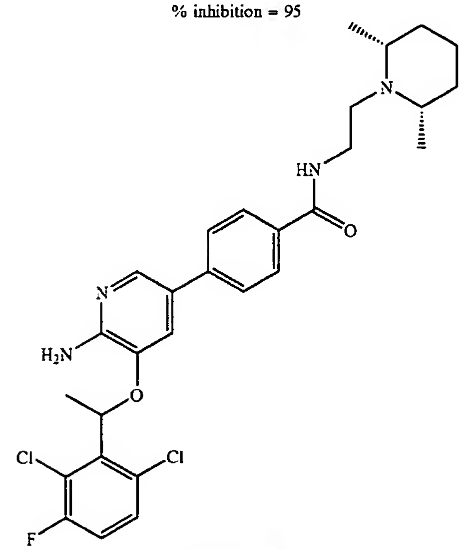
TABLE 5-continued



% inhibition = 53

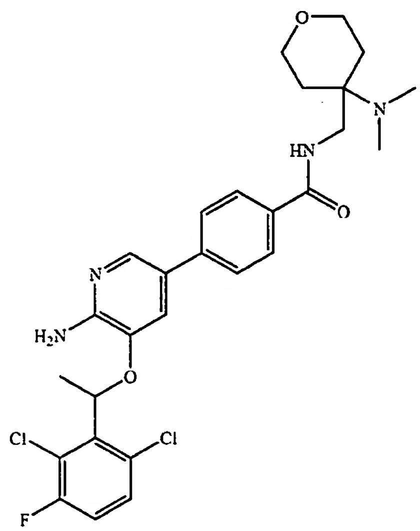


% inhibition = 95

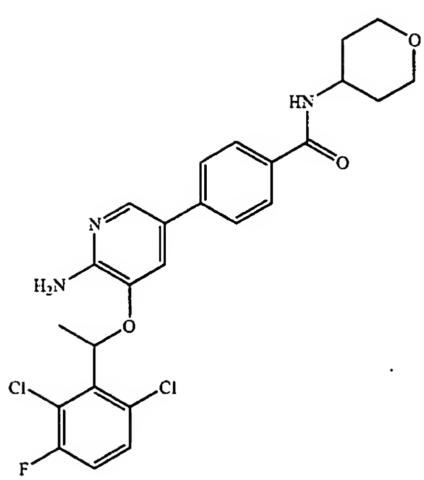


% inhibition = 77

TABLE 5-continued

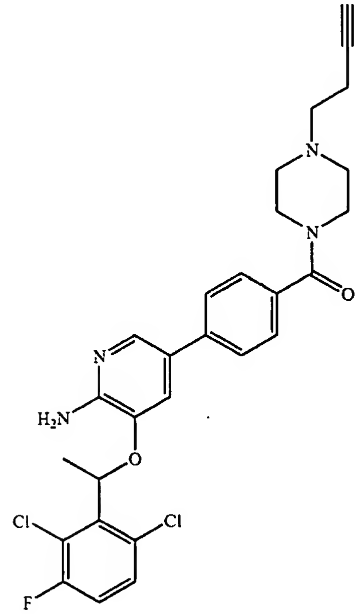


% inhibition = 66

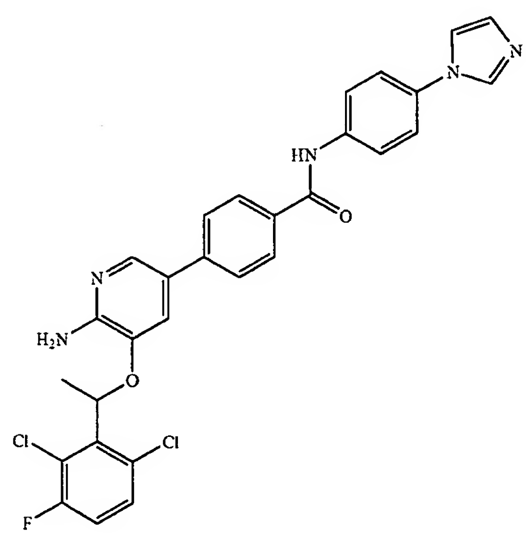


% inhibition = 73

TABLE 5-continued

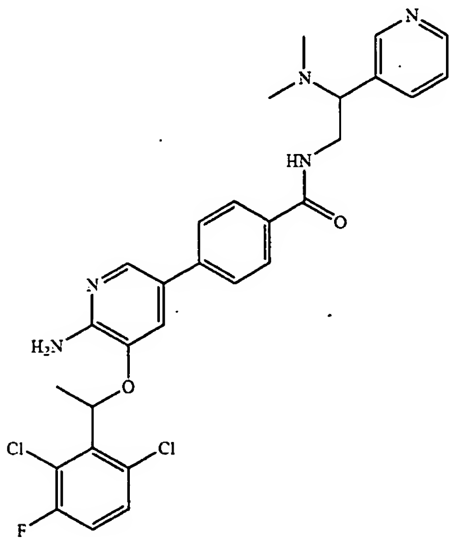


% inhibition = 77

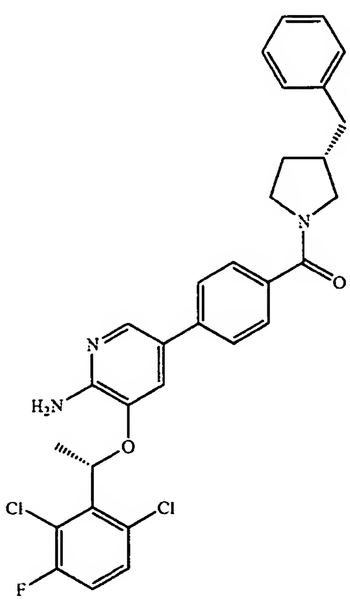


% inhibition = 63

TABLE 5-continued



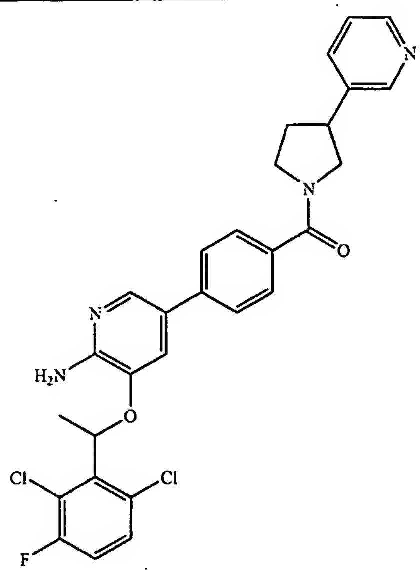
% inhibition = 78



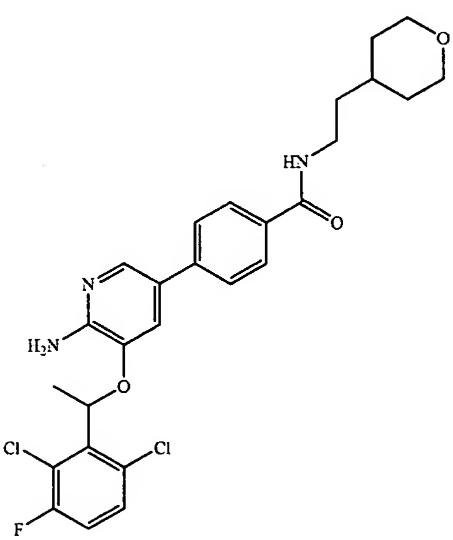
% inhibition = 59

TABLE 5-continued

Section K: Examples L-161 to L-176

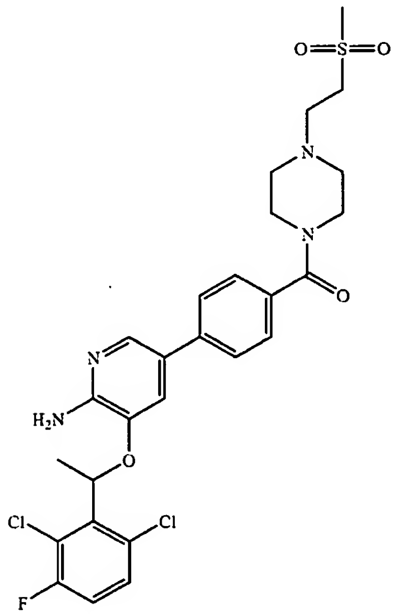


% inhibition = 79

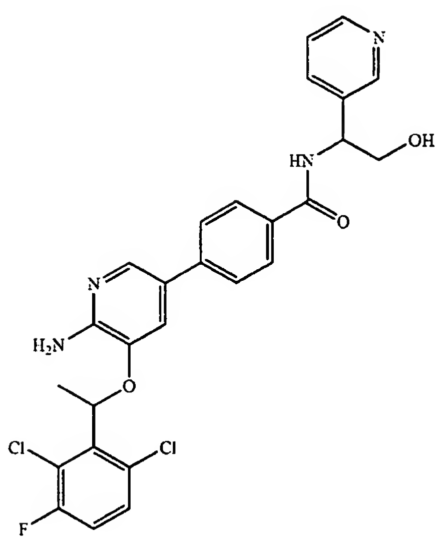


% inhibition = 66

TABLE 5-continued

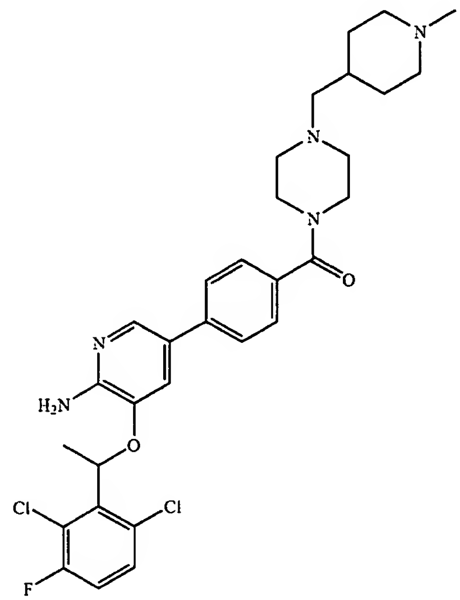


% inhibition = 83

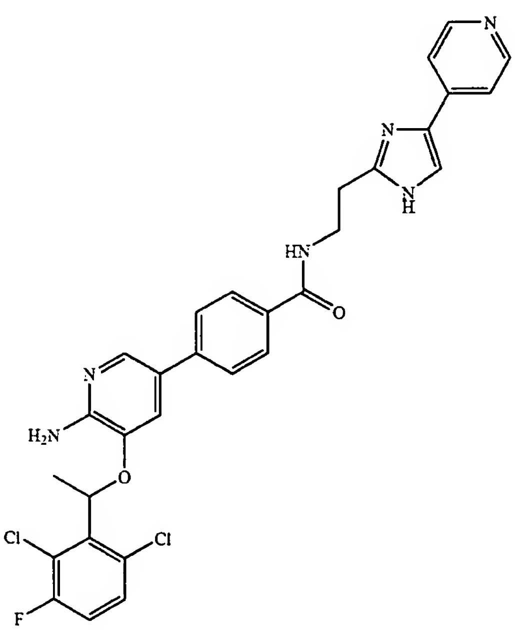


% inhibition = 61

TABLE 5-continued

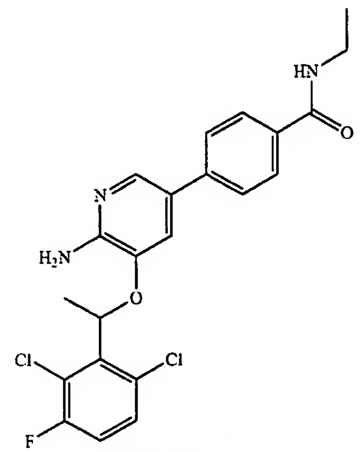


% inhibition = 88

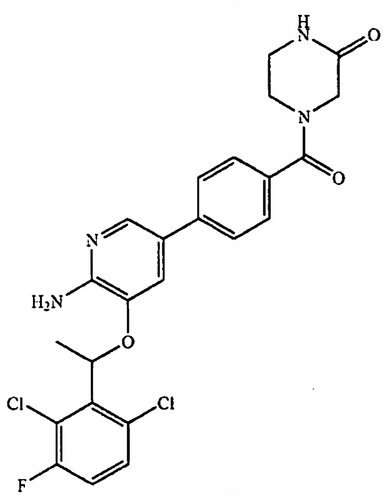


% inhibition = 67

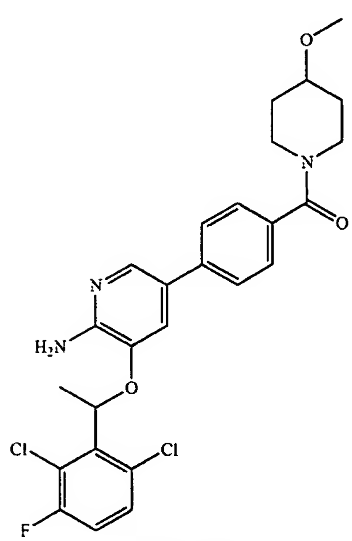
TABLE 5-continued



% inhibition = 66

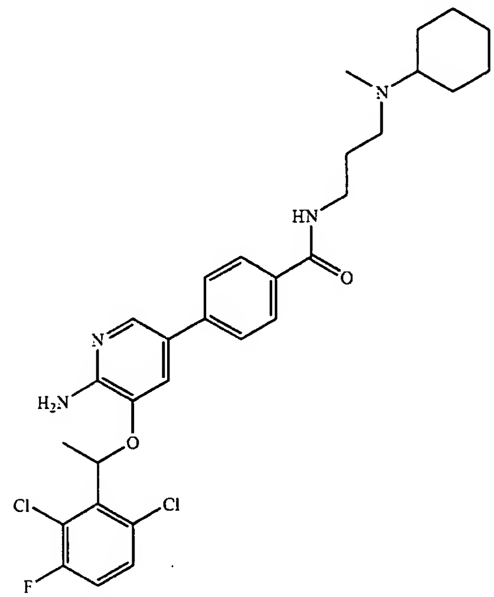


% inhibition = 90

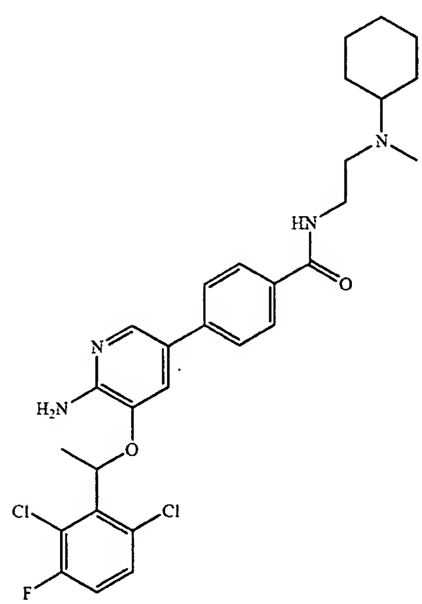


% inhibition = 79

TABLE 5-continued

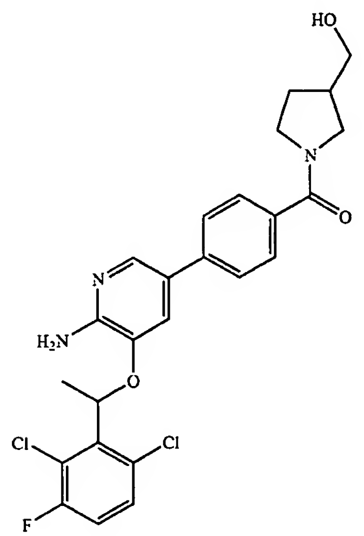


% inhibition = 77

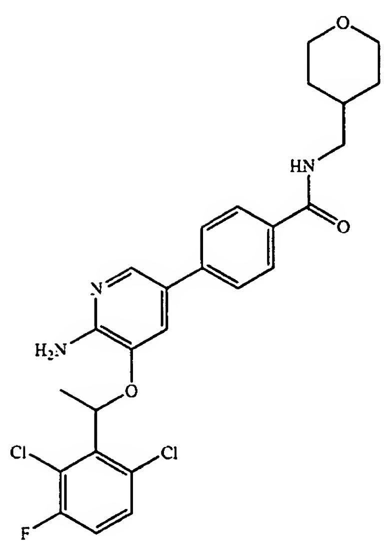


% inhibition = 69

TABLE 5-continued

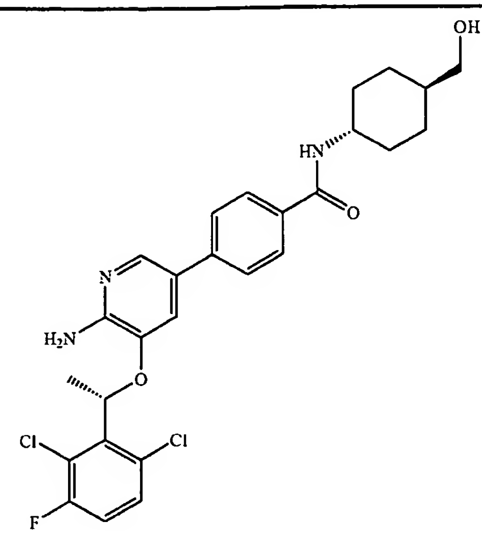


% inhibition = 79

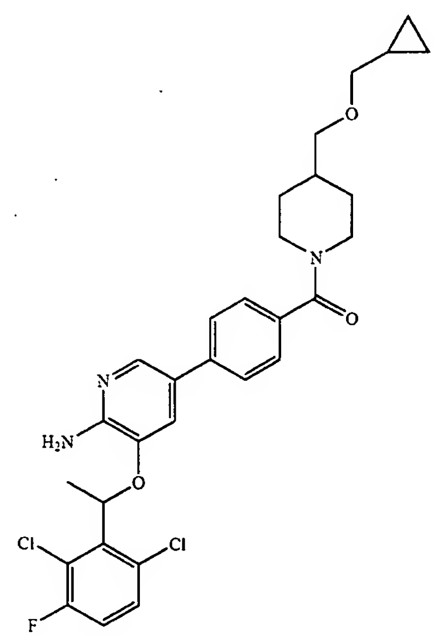


% inhibition = 63

TABLE 5-continued

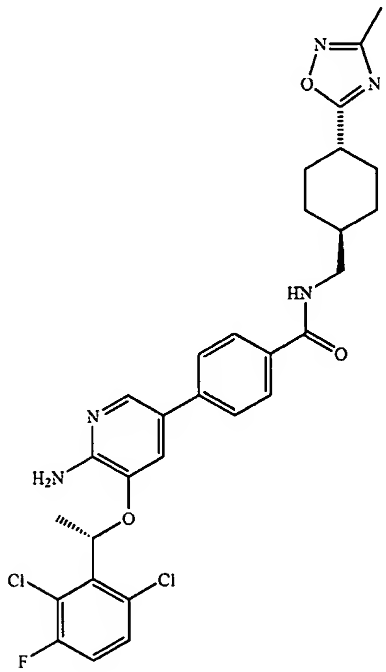


% inhibition = 68



% inhibition = 60

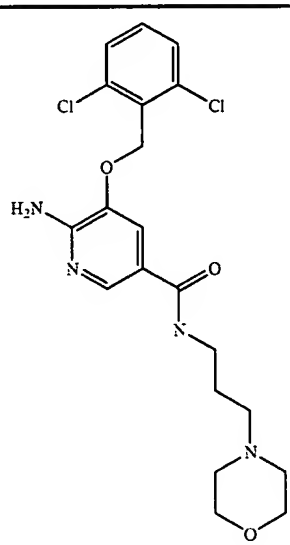
TABLE 5-continued



% inhibition = 51

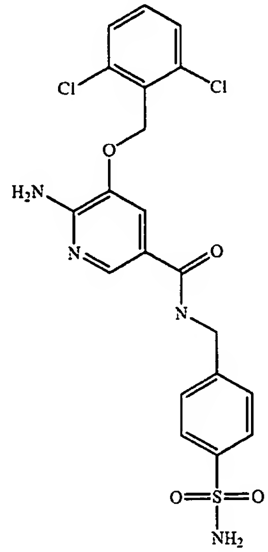
TABLE 6

Section A: Examples L-177 to L-192

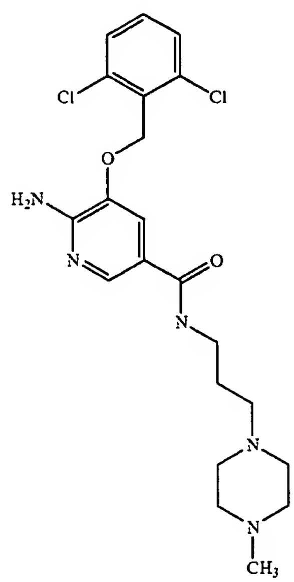


% Inhibition = 26

TABLE 6-continued

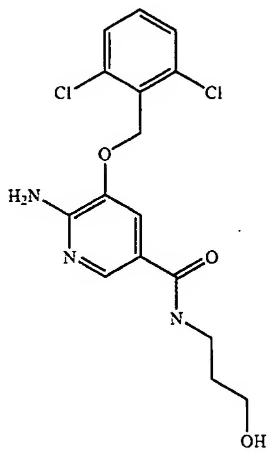


% Inhibition = 30

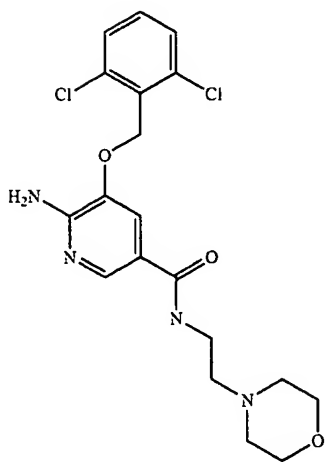


% Inhibition = 24

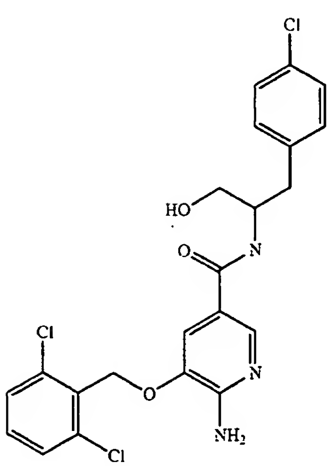
TABLE 6-continued



% Inhibition = 26

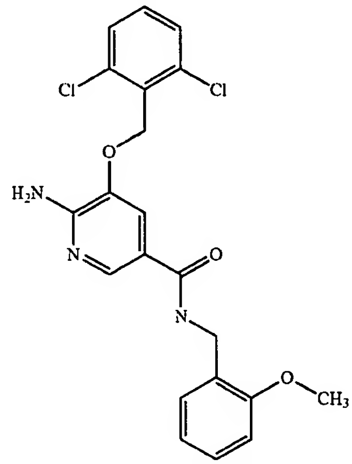


% Inhibition = 31

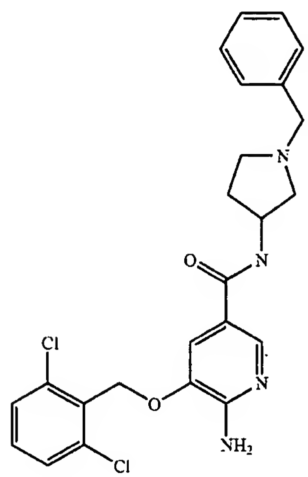


% Inhibition = 27

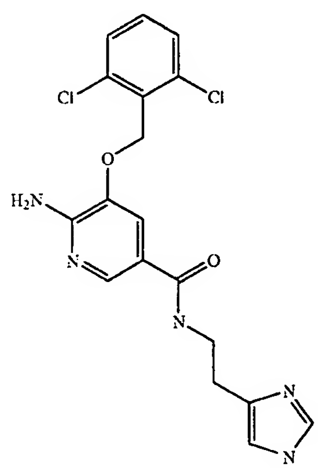
TABLE 6-continued



% Inhibition = 32

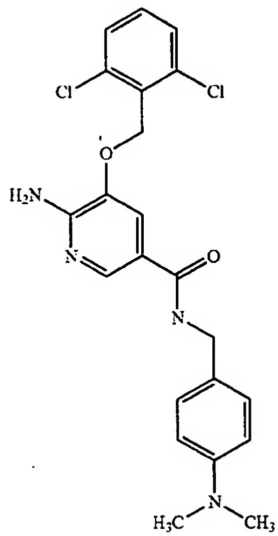


% Inhibition = 27

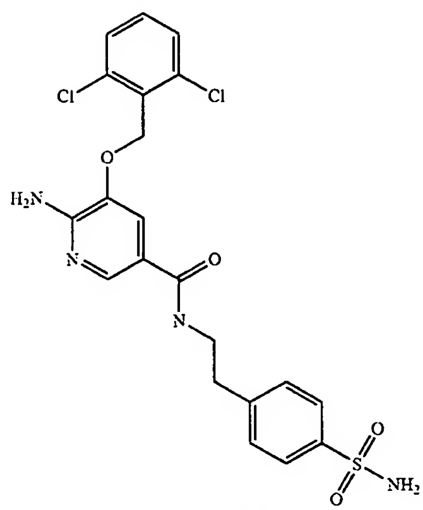


% Inhibition = 29

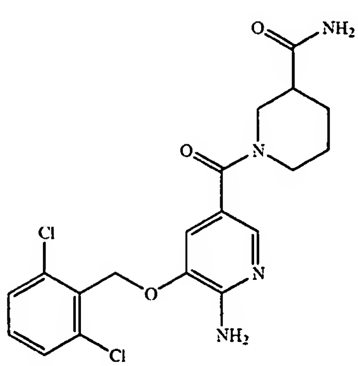
TABLE 6-continued



% Inhibition = 30

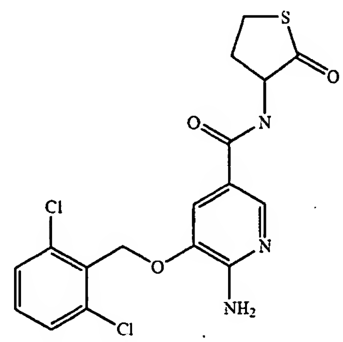


% Inhibition = 30

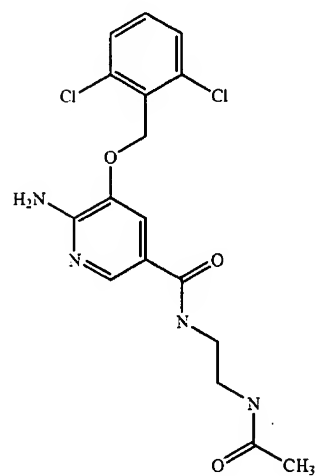


% Inhibition = 39

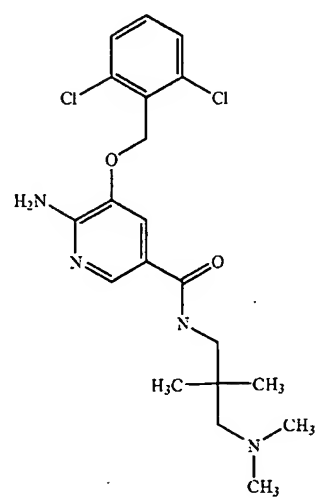
TABLE 6-continued



% Inhibition = 35

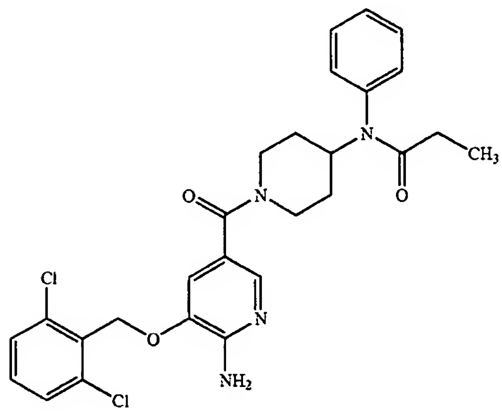


% Inhibition = 35



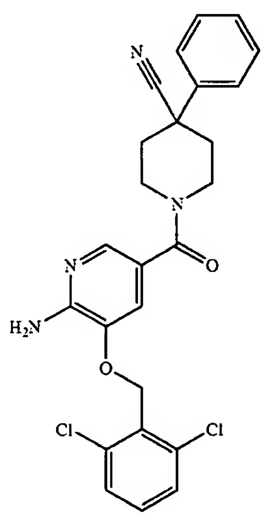
% Inhibition = 38

TABLE 6-continued

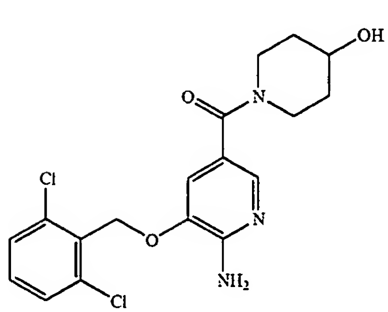


% Inhibition = 44

Section B: Examples L-193 to L-208

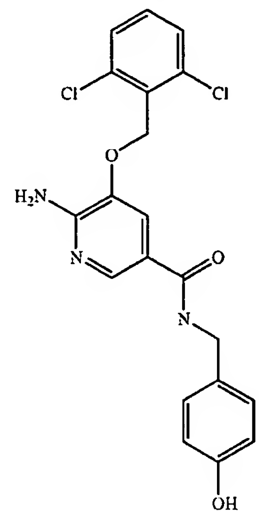


% Inhibition = 37

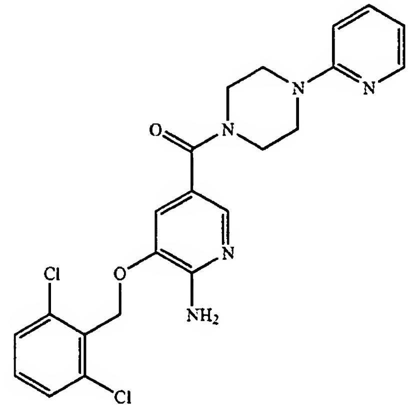


% Inhibition = 35

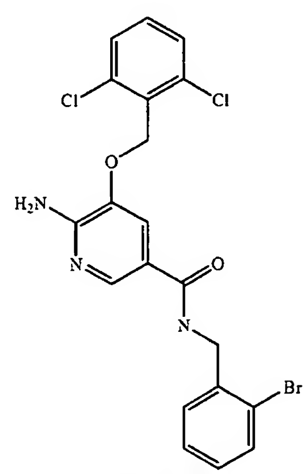
TABLE 6-continued



% Inhibition = 37

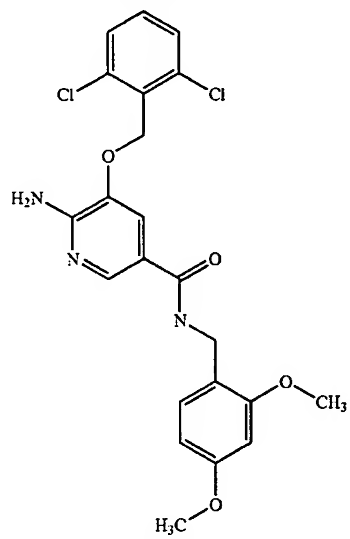


% Inhibition = 34

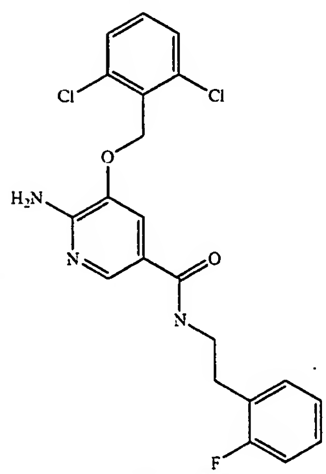


% Inhibition = 36

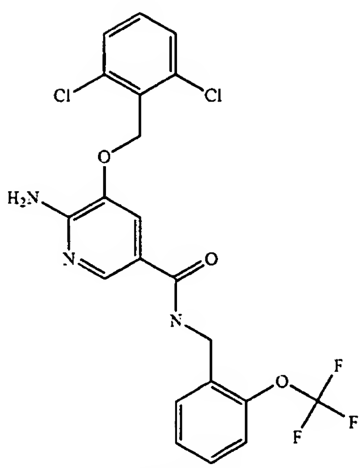
TABLE 6-continued



% Inhibition = 59

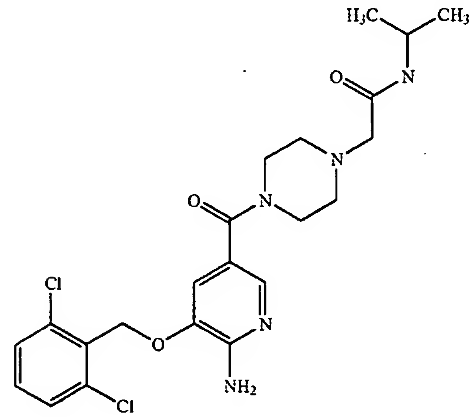


% Inhibition = 33

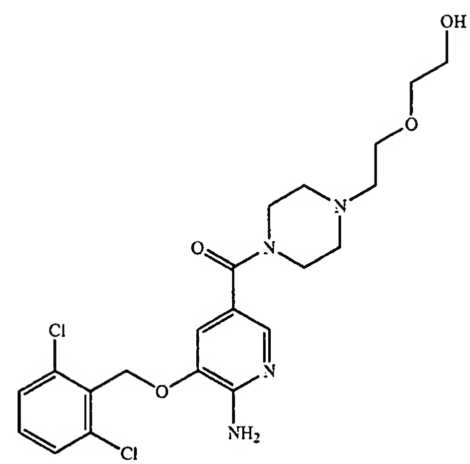


% Inhibition = 31

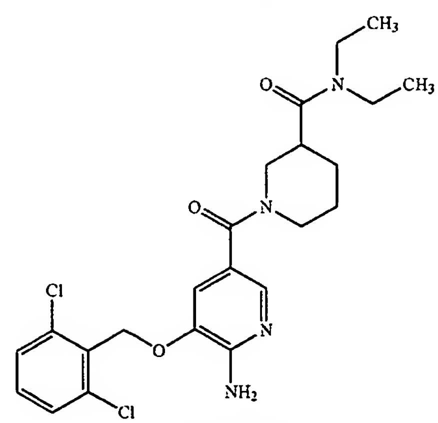
TABLE 6-continued



% Inhibition = 30

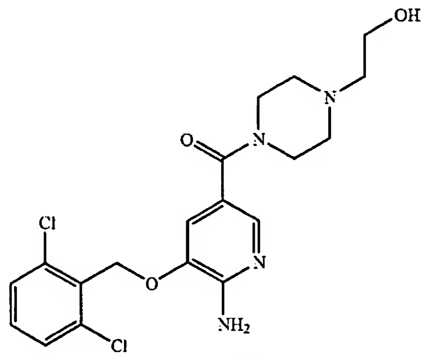


% Inhibition = 33

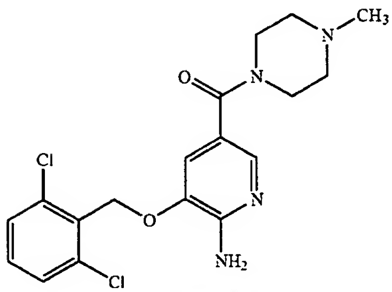


% Inhibition = 33

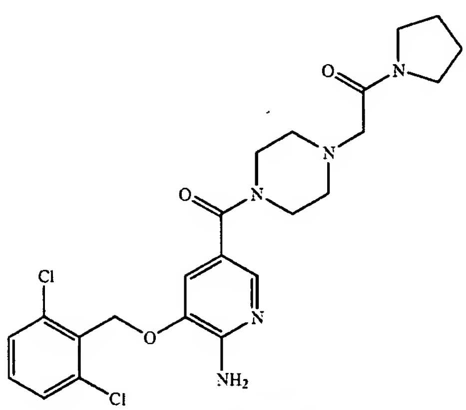
TABLE 6-continued



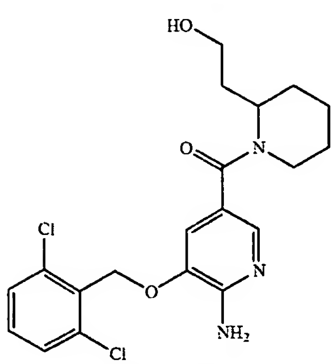
% Inhibition = 51



% Inhibition = 32

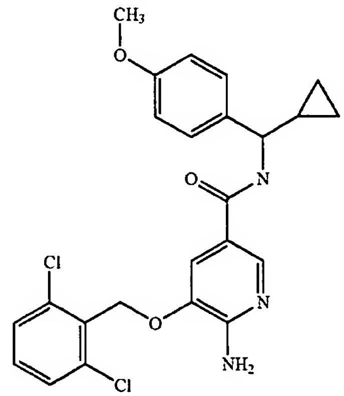


% Inhibition = 32



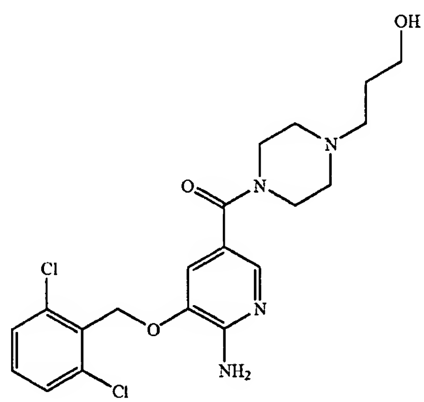
% Inhibition = 33

TABLE 6-continued

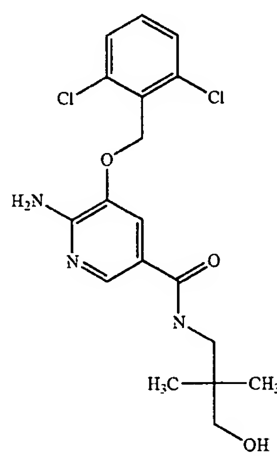


% Inhibition = 27

Section C: Examples L-209 to L-224

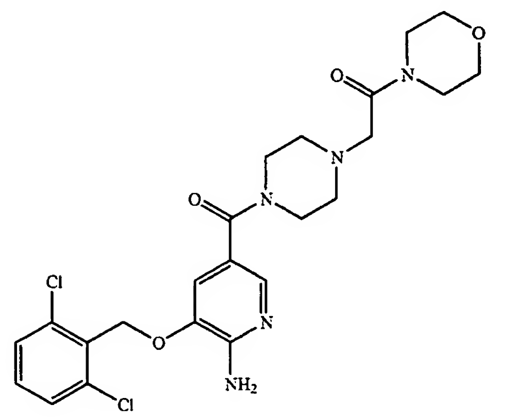


% Inhibition = 31

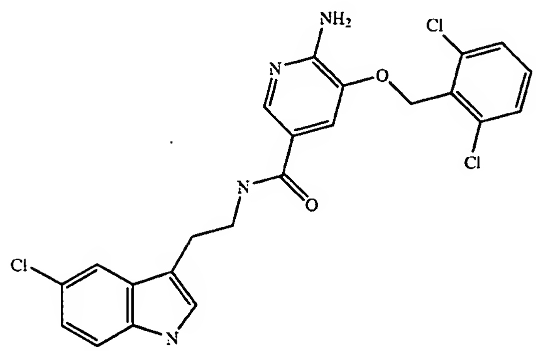


% Inhibition = 39

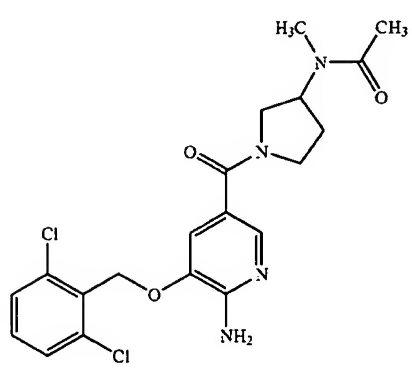
TABLE 6-continued



% Inhibition = 31

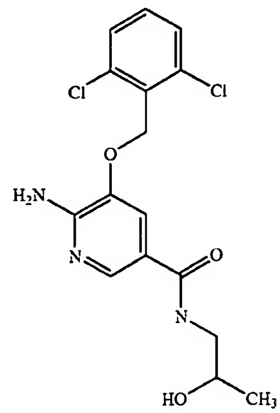


% Inhibition = 36

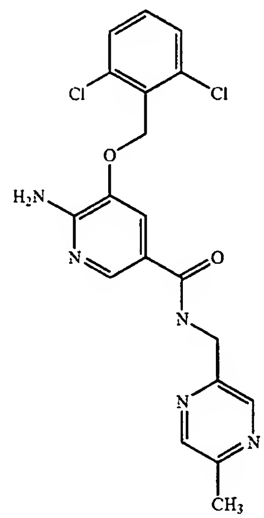


% Inhibition = 31

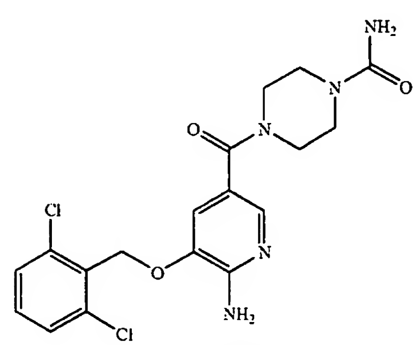
TABLE 6-continued



% Inhibition = 49

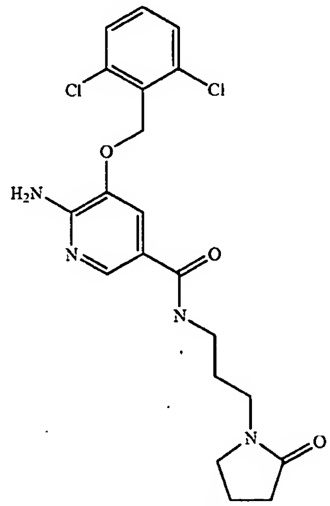


% Inhibition = 33

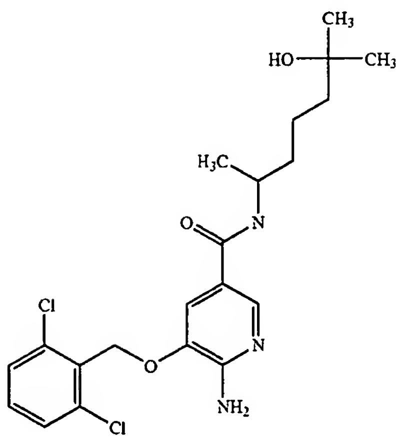


% Inhibition = 29

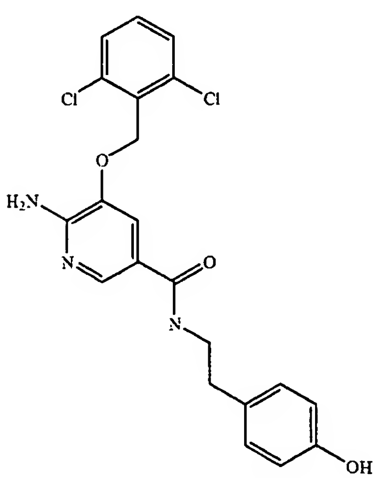
TABLE 6-continued



% Inhibition = 34



% Inhibition = 35



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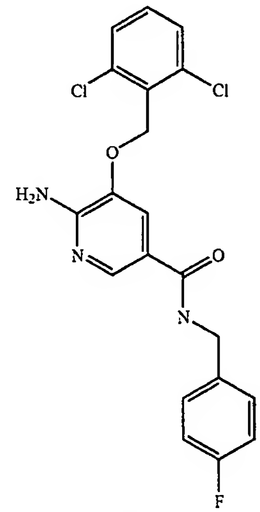
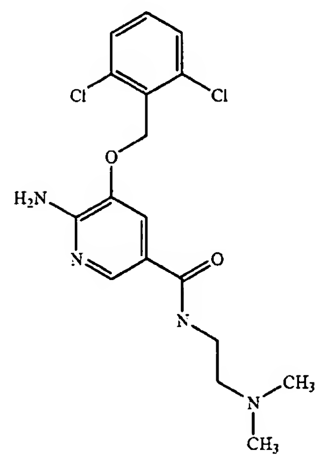
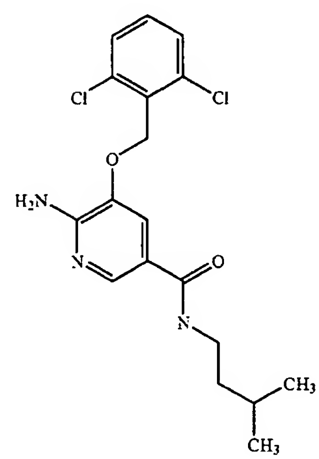


% Inhibition = 32



% Inhibition = 29



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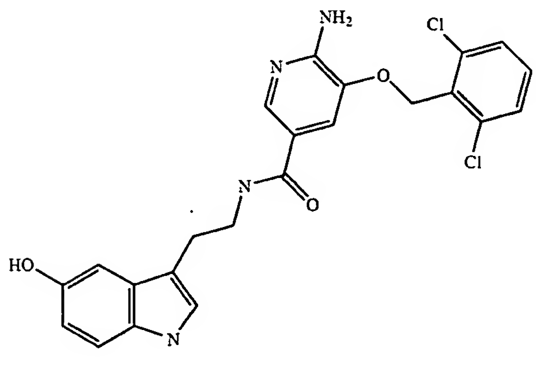

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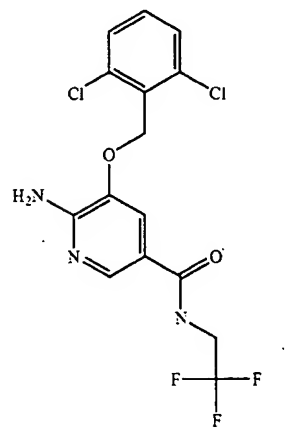
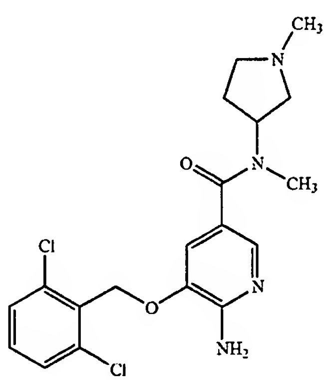


% Inhibition = 30

Section D: Examples L-225 to L-240



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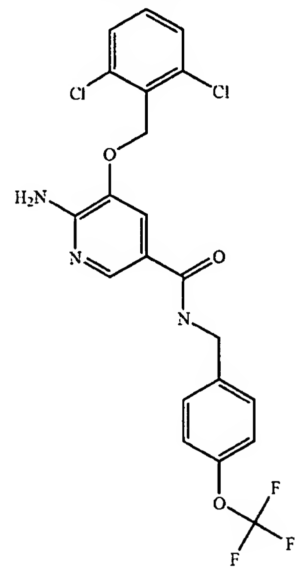

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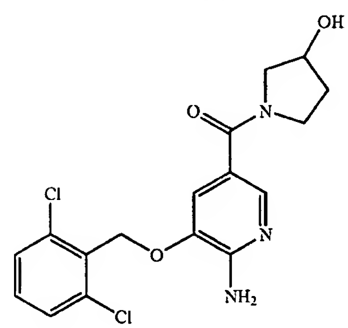

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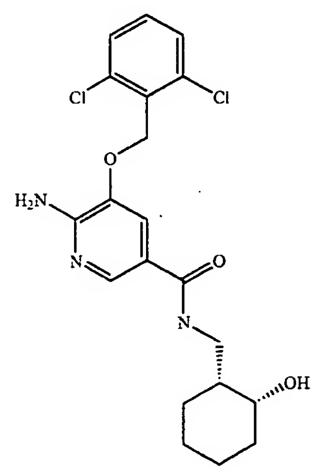

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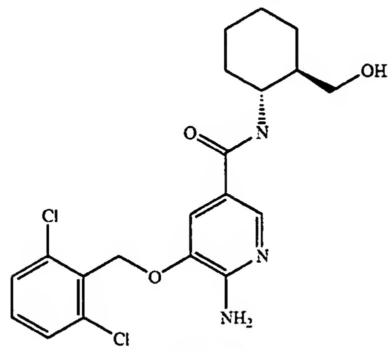

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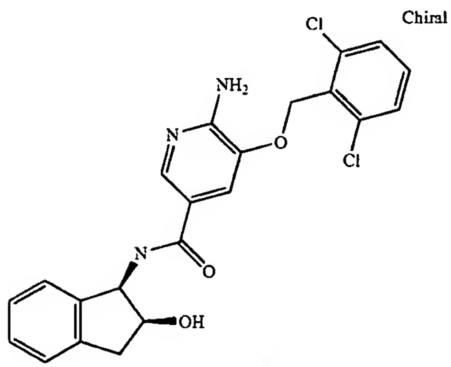
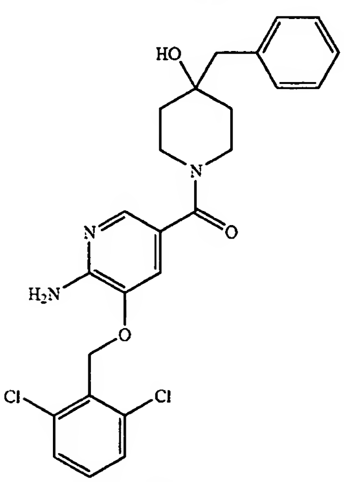
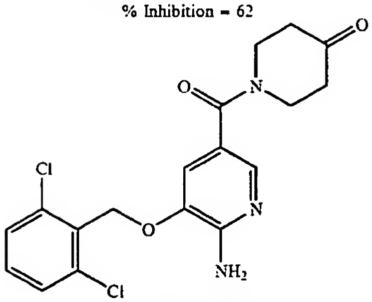


% Inhibition = 23

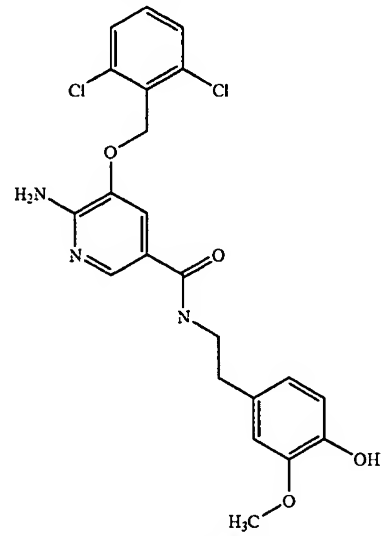


% Inhibition = 62

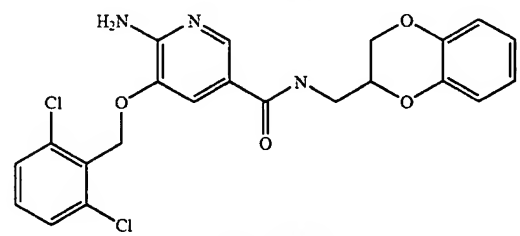


% Inhibition = 44

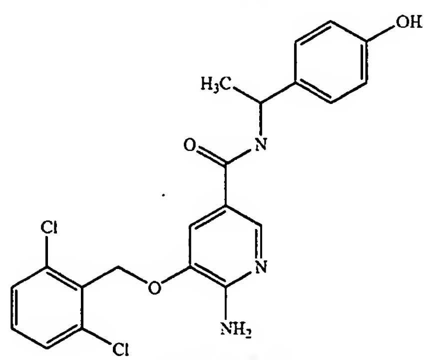
TABLE 6-continued



% Inhibition = 32



% Inhibition = 34



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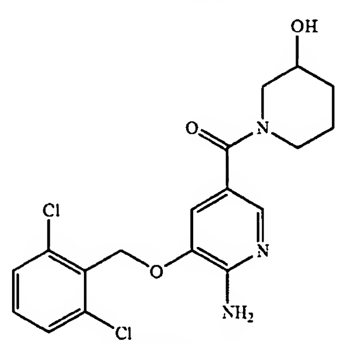

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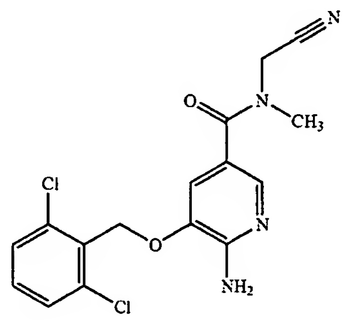
TABLE 6-continued



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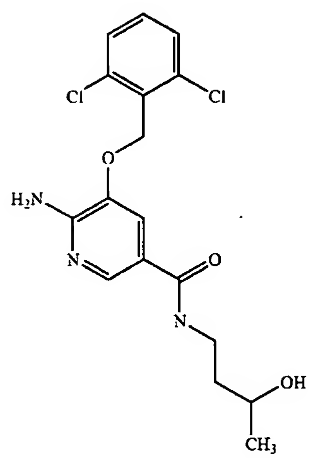

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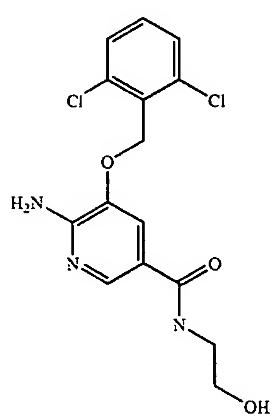

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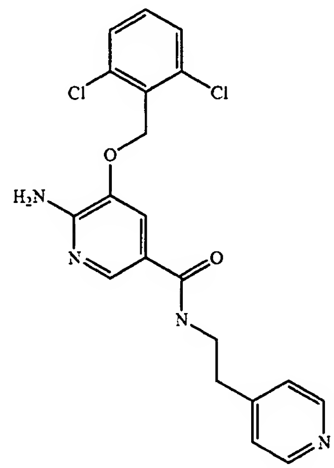
TABLE 6-continued



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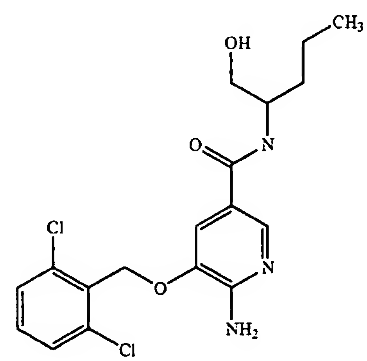
Section E: Examples L-241 to L-256



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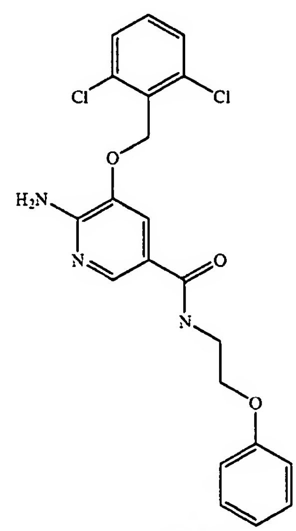

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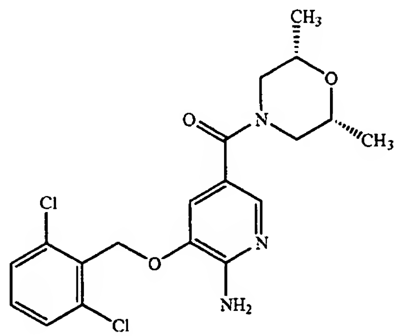

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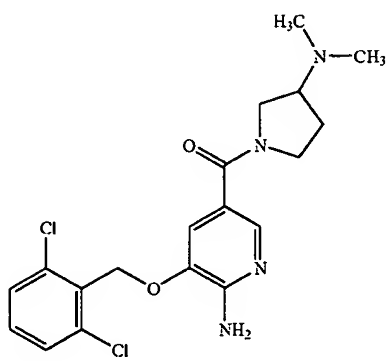

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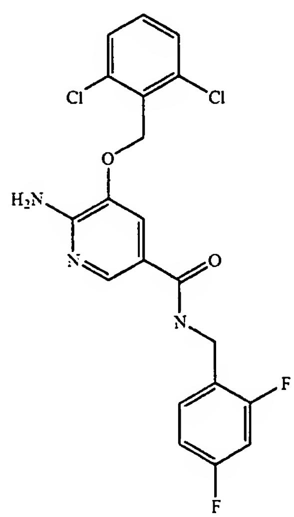

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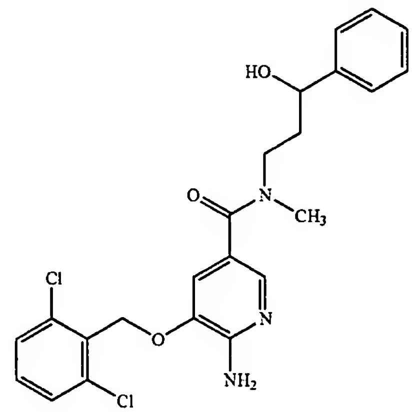
TABLE 6-continued



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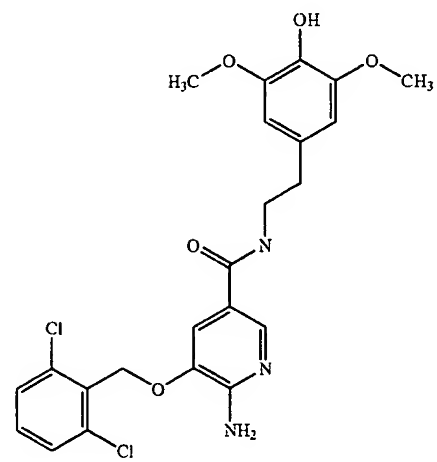

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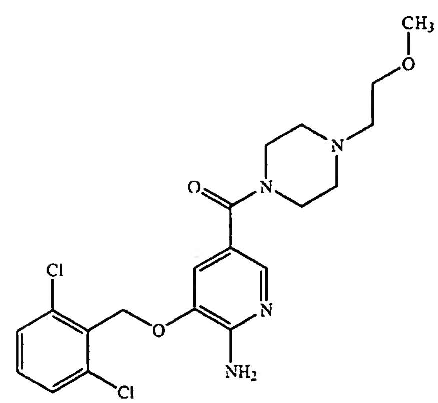
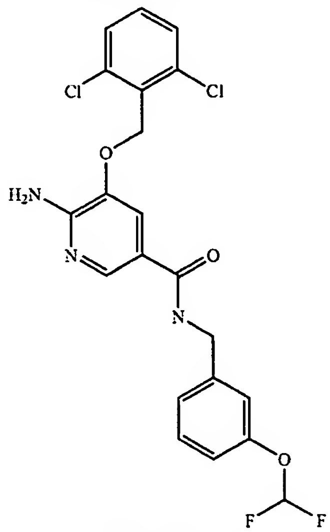


% Inhibition = 27

TABLE 6-continued



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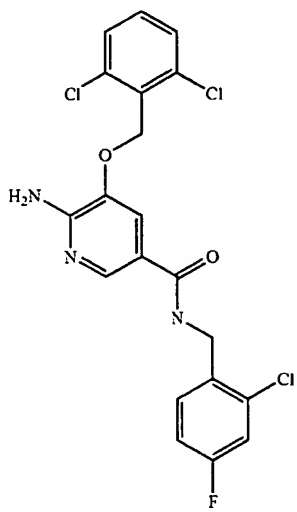

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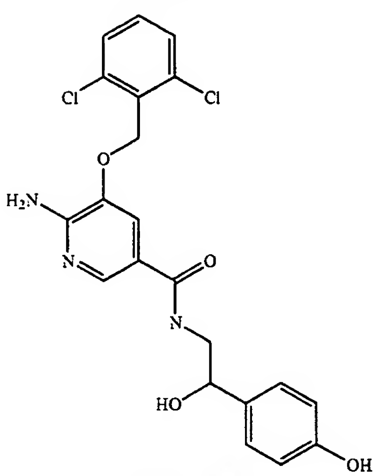
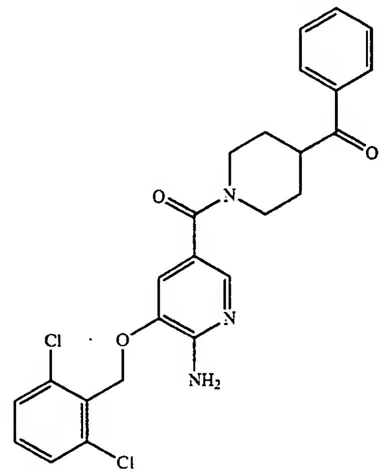
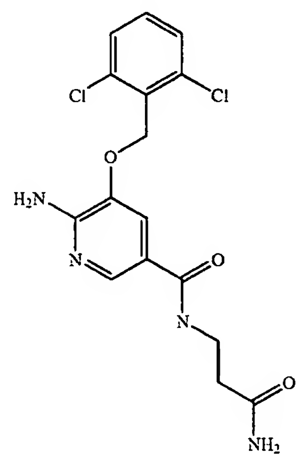


% Inhibition = 29

TABLE 6-continued



% Inhibition = 32



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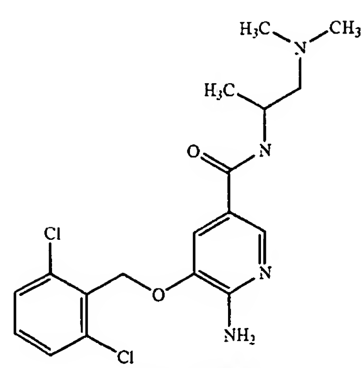

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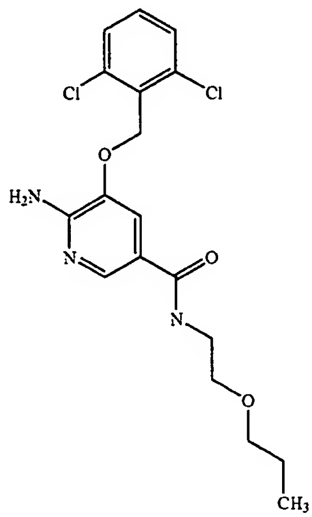
TABLE 6-continued



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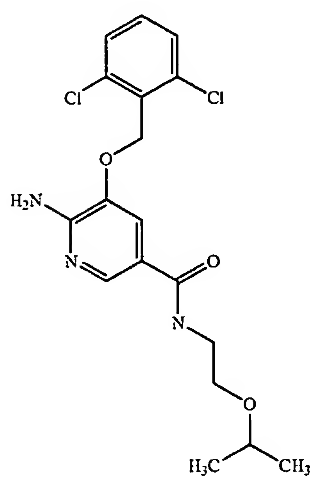

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Section F: Examples L-257 to L-272

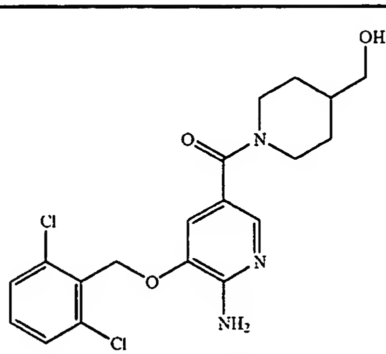

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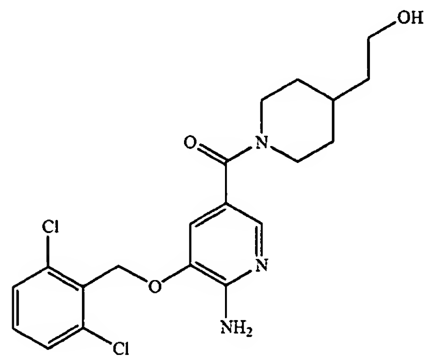
TABLE 6-continued



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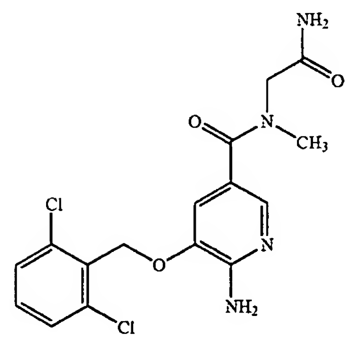

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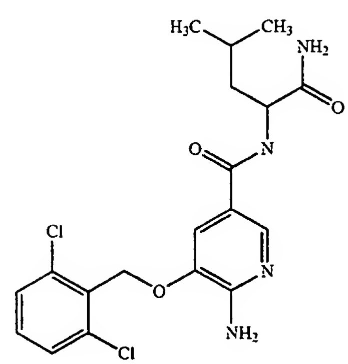

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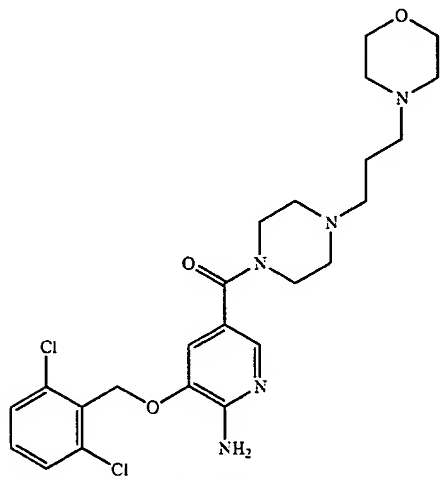

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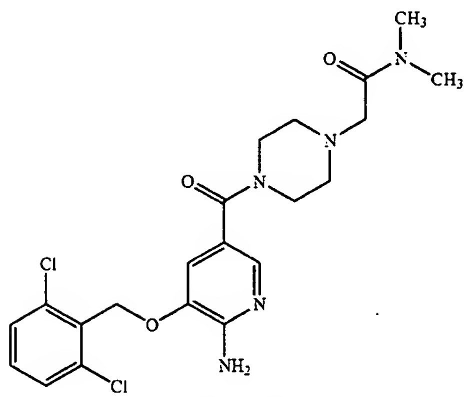

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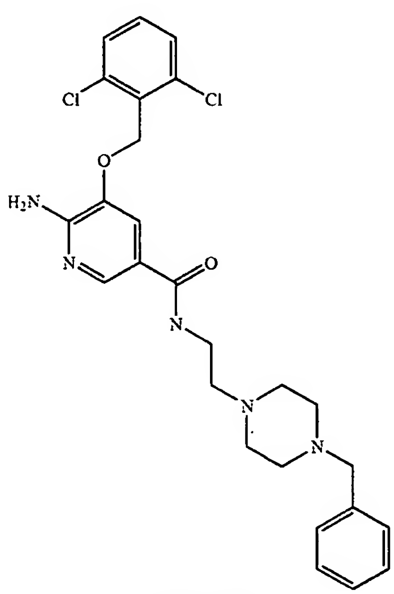

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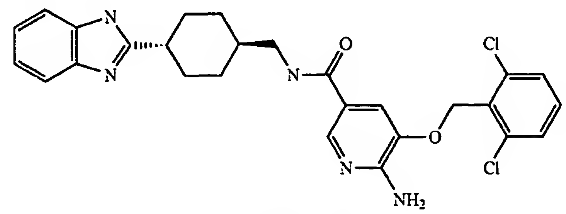
TABLE 6-continued



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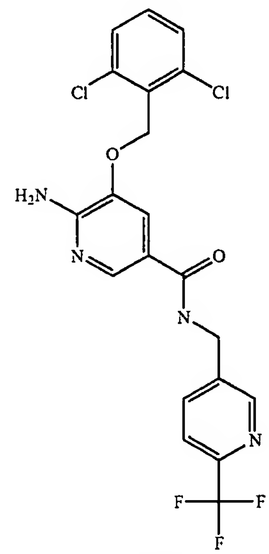
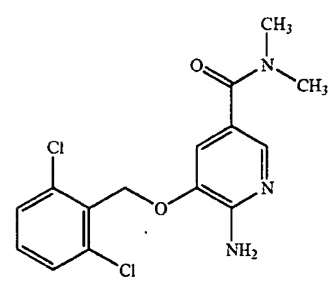


% Inhibition = 17



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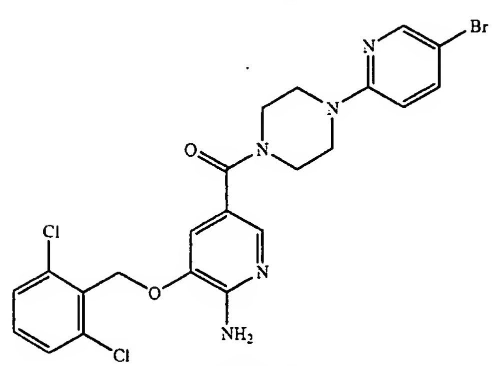

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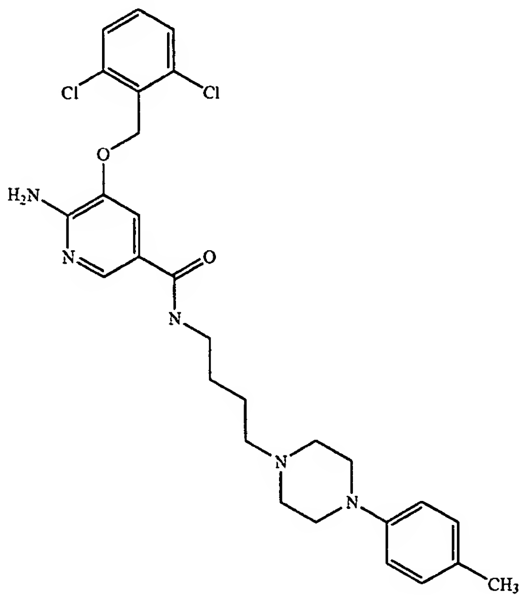
TABLE 6-continued



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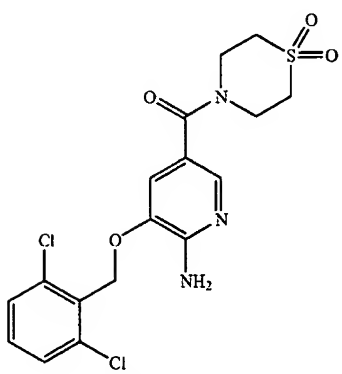

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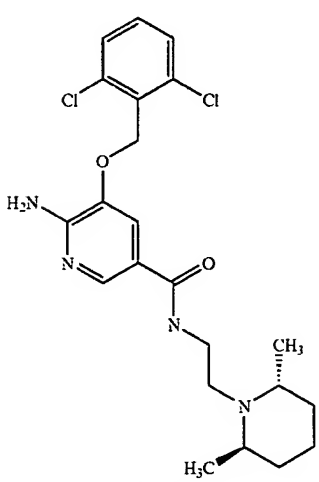

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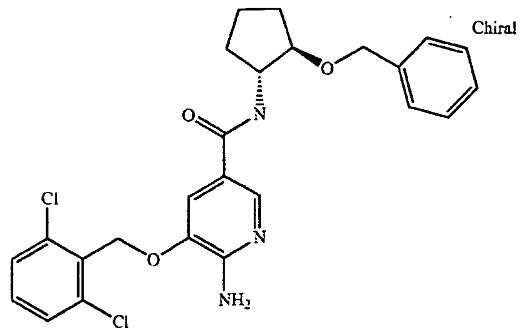
TABLE 6-continued



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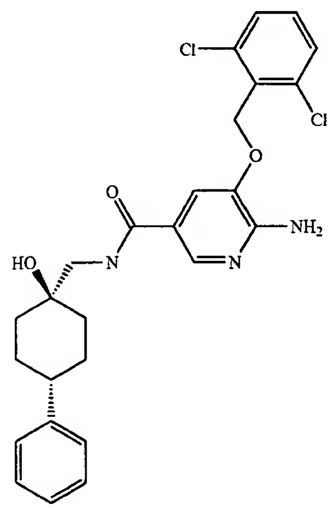

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Section G: Examples L-273 to L-288

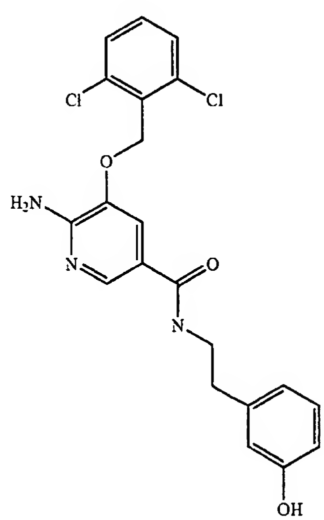

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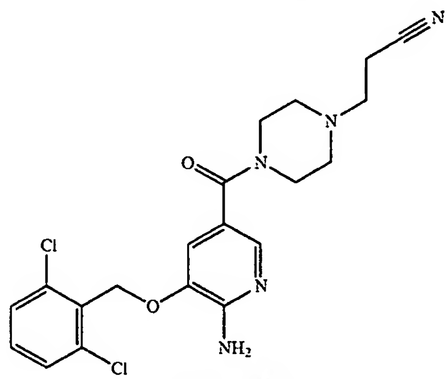
TABLE 6-continued



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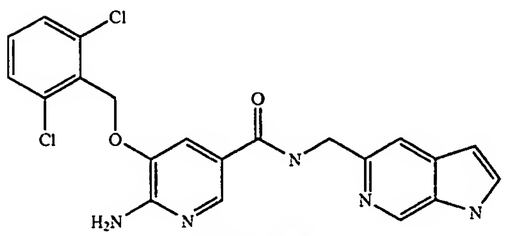

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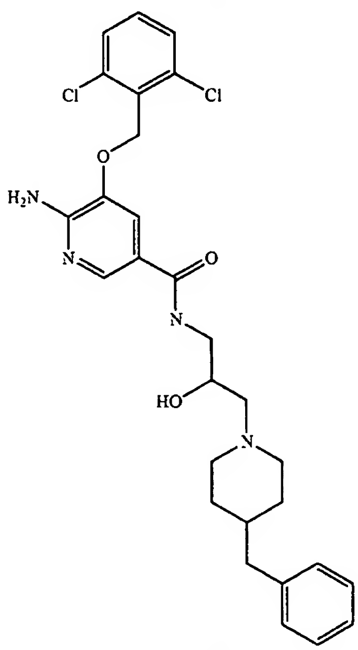

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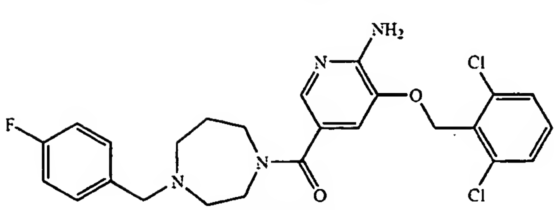

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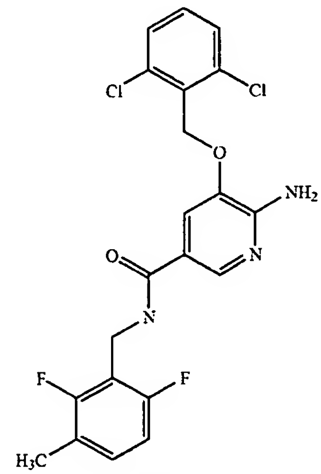
TABLE 6-continued



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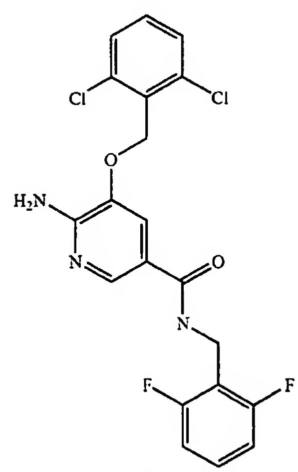

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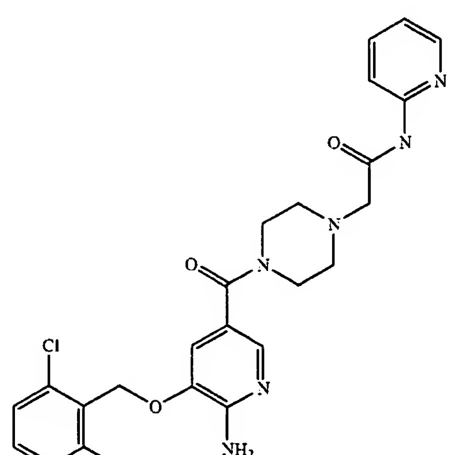
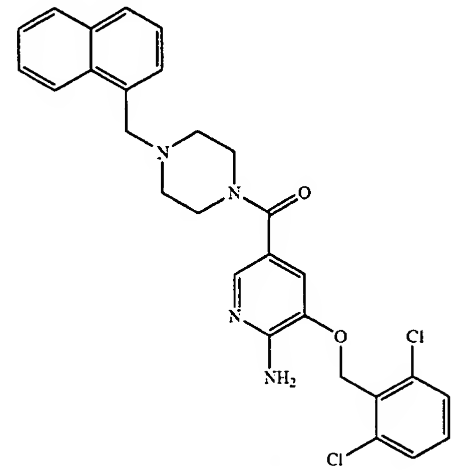


% Inhibition = 56

TABLE 6-continued



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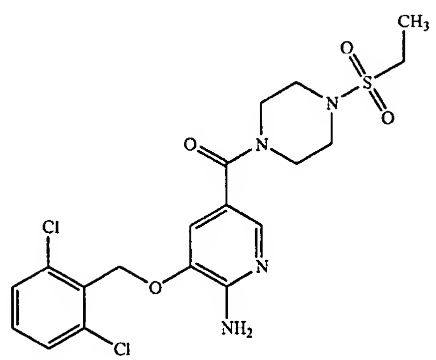

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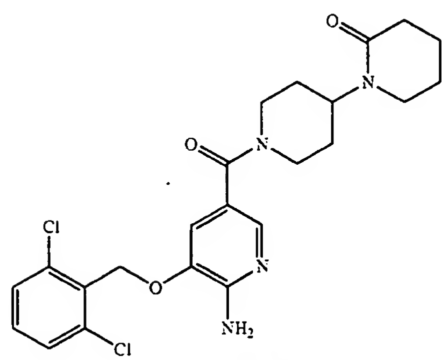

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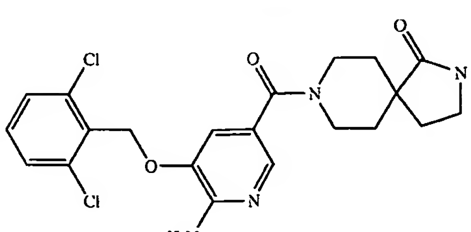

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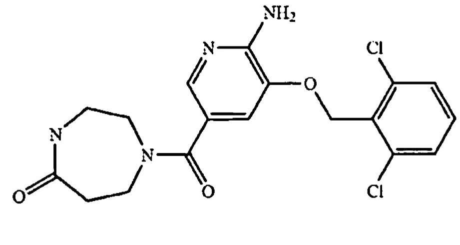
TABLE 6-continued



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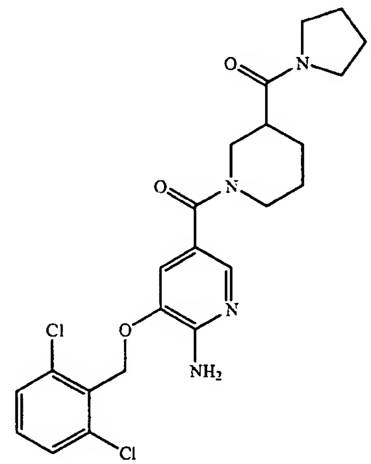

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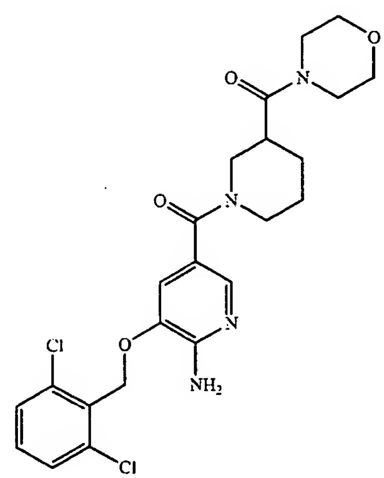

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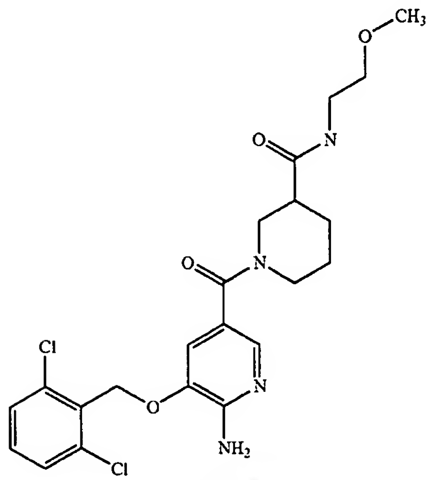
TABLE 6-continued



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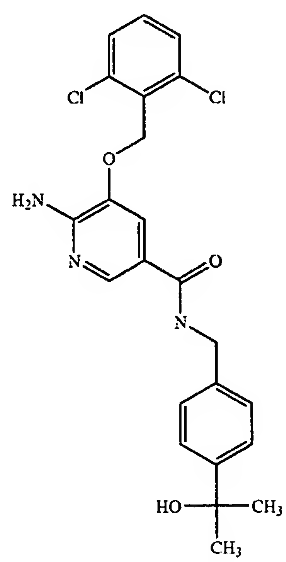
Section G: Examples L-289 to L-304



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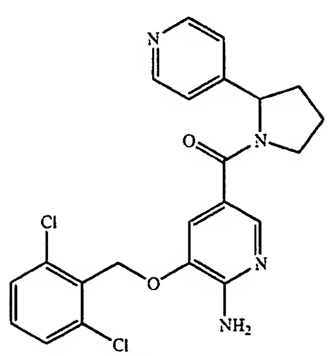

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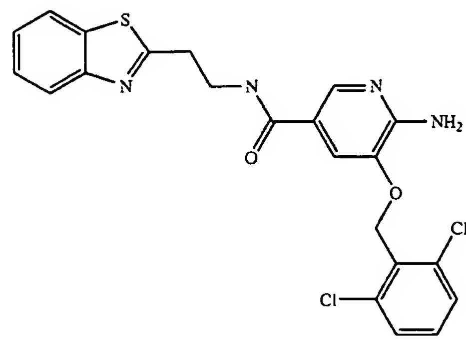
TABLE 6-continued



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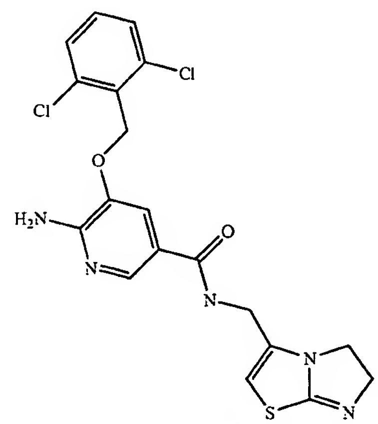

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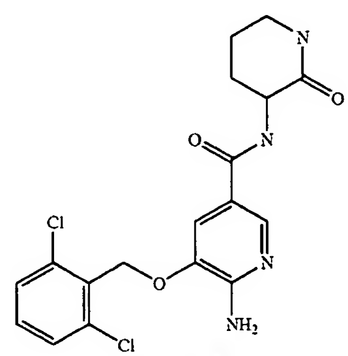

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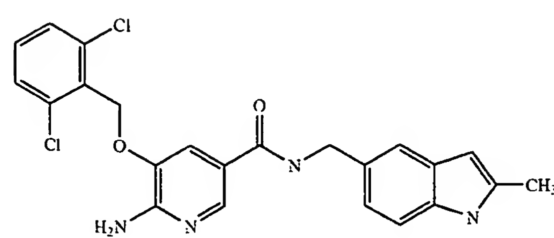

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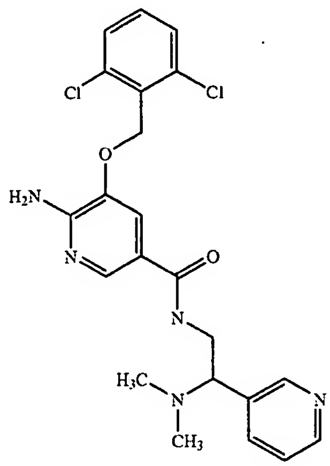
TABLE 6-continued



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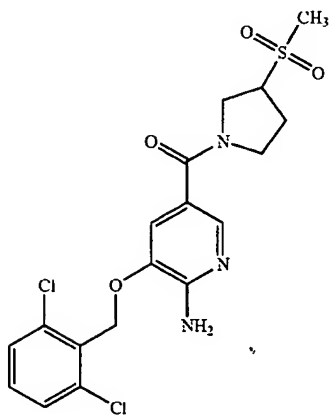

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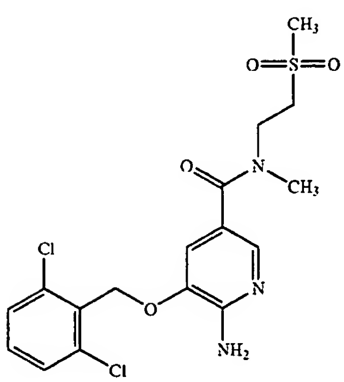

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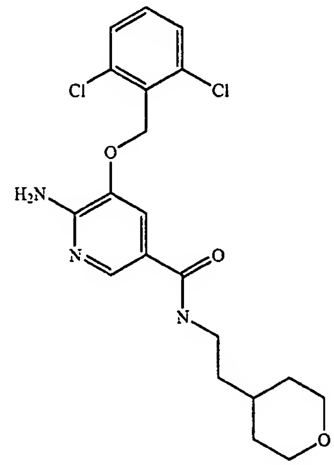

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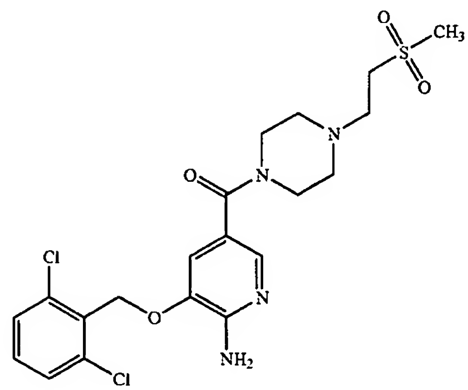

% Inhibition = 25

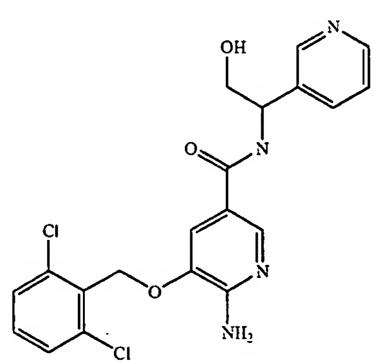

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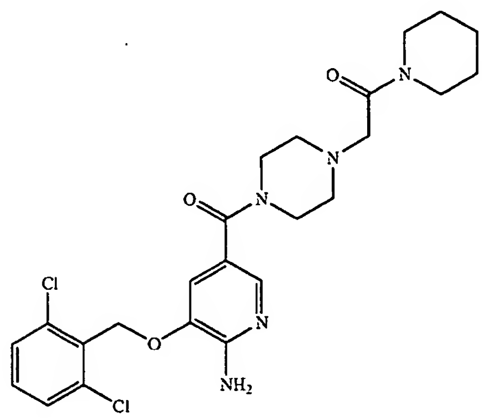
TABLE 6-continued



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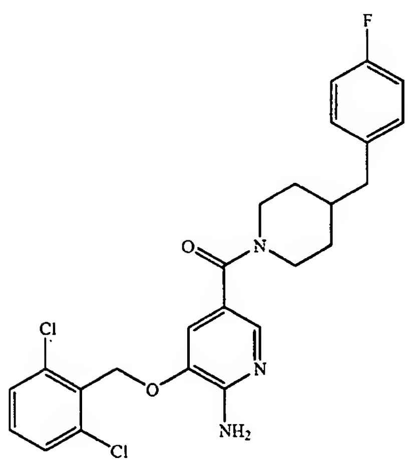

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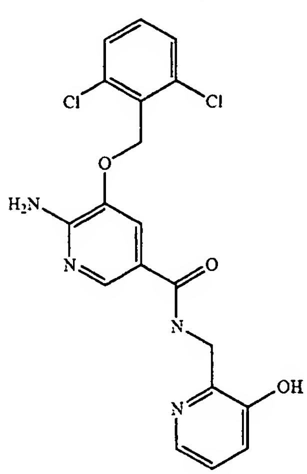

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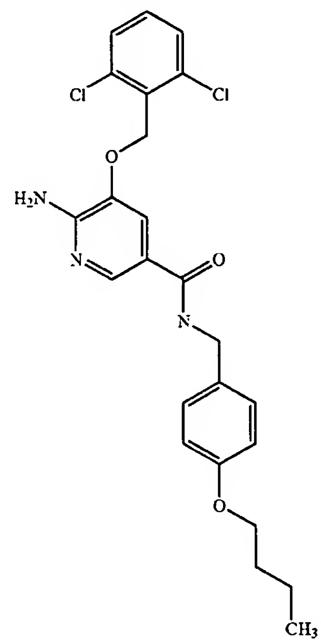

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Section I: Examples L-305 to L-320

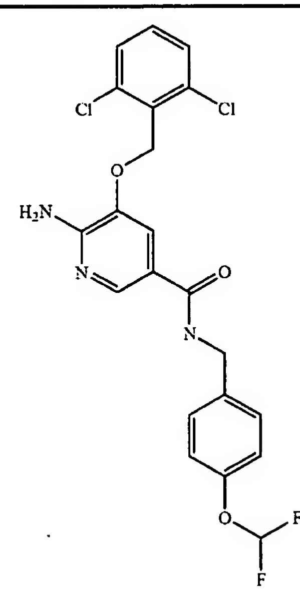

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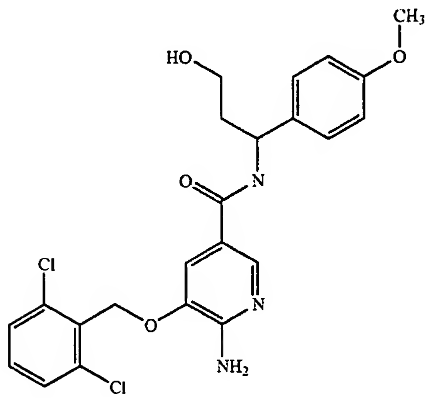
TABLE 6-continued



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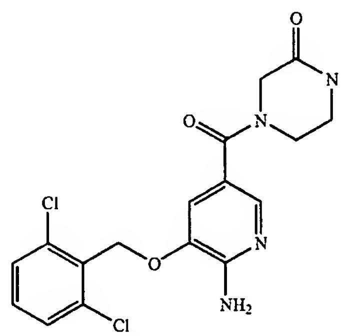

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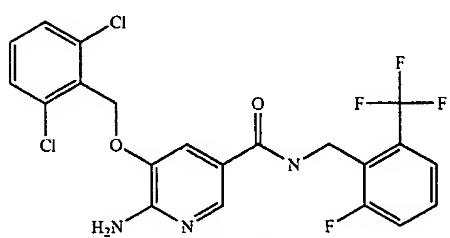

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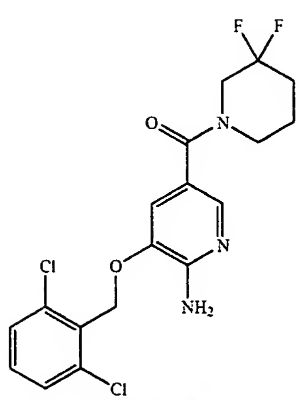

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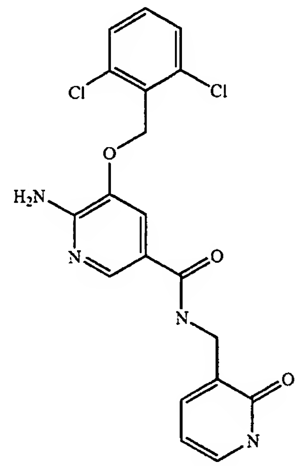
TABLE 6-continued



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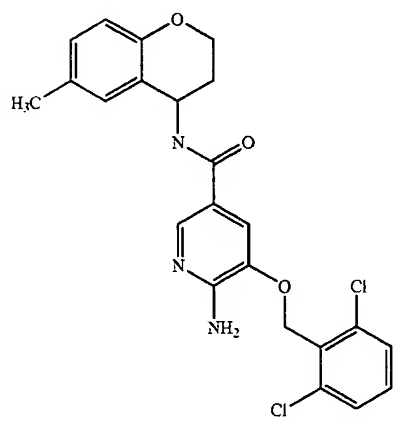

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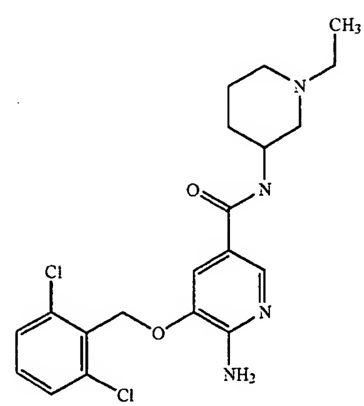

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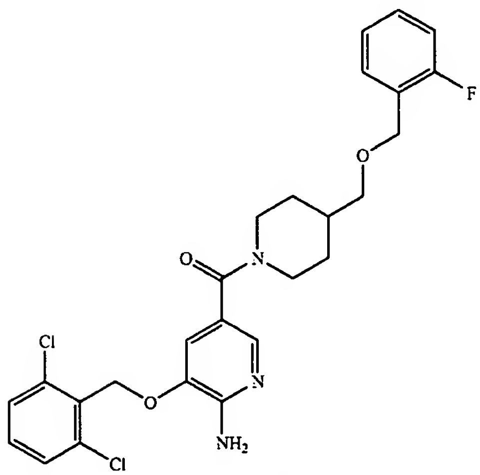
TABLE 6-continued



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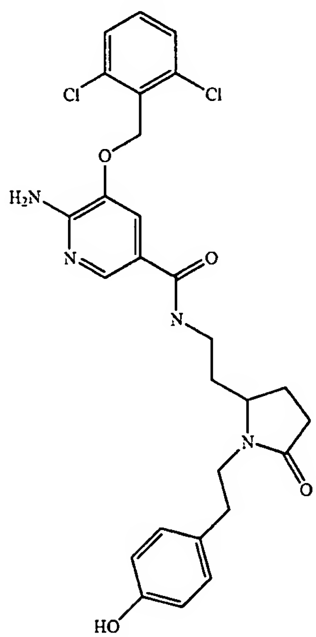

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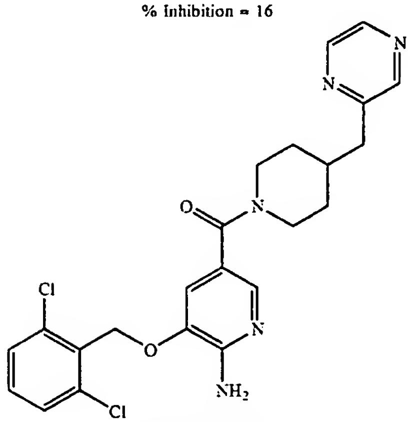

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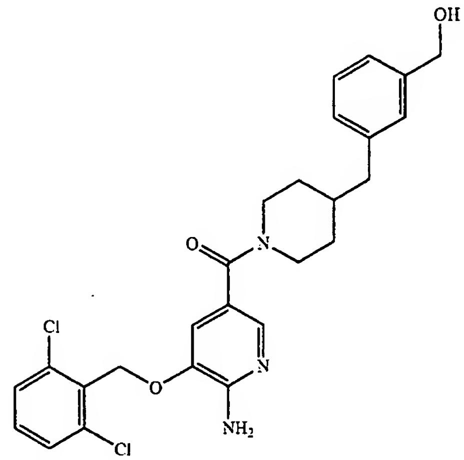
TABLE 6-continued



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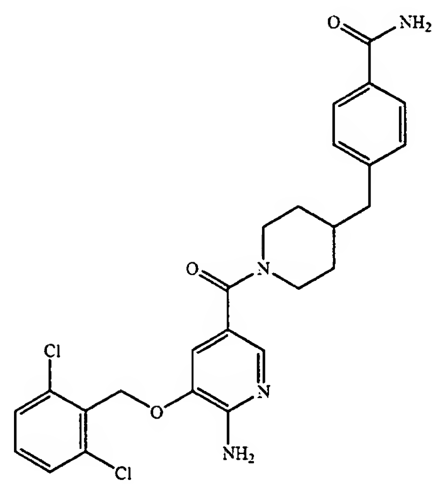

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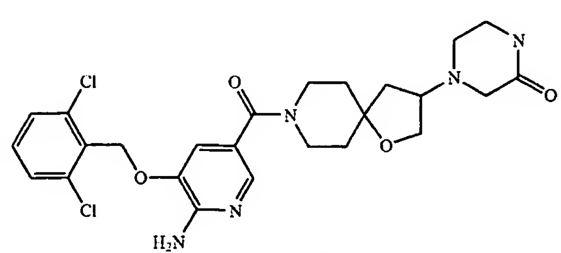

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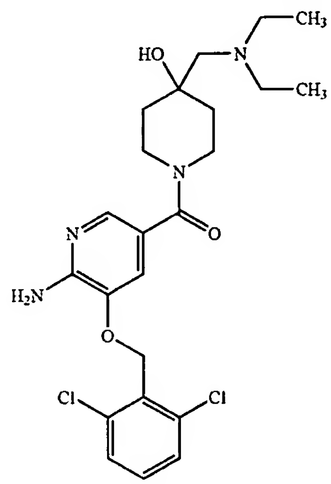
TABLE 6-continued



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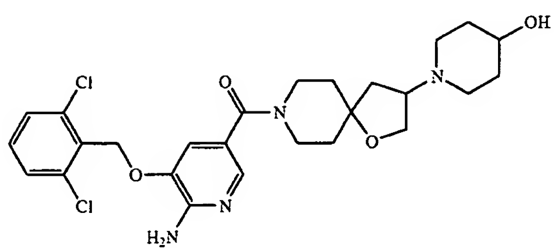

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Section J: Examples L-321 to L-336

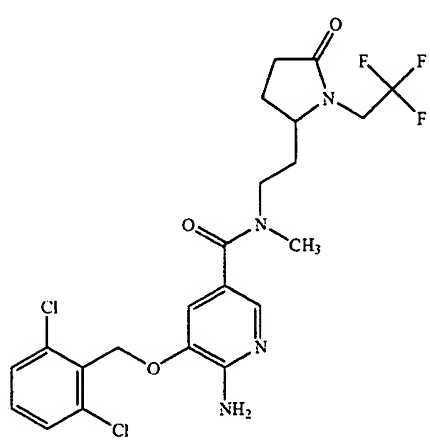

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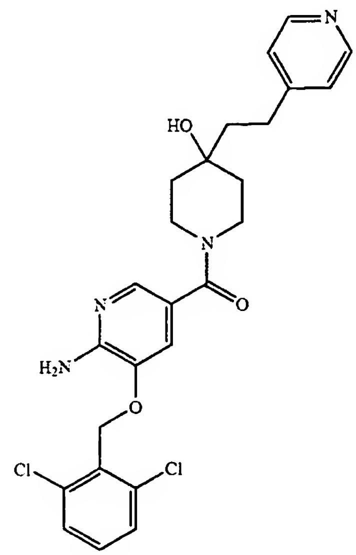
TABLE 6-continued



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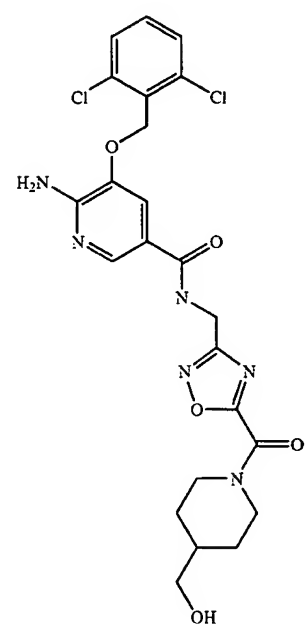

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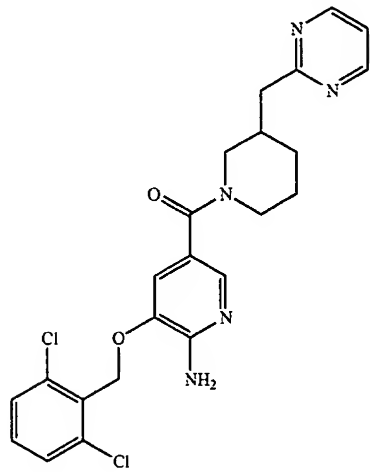

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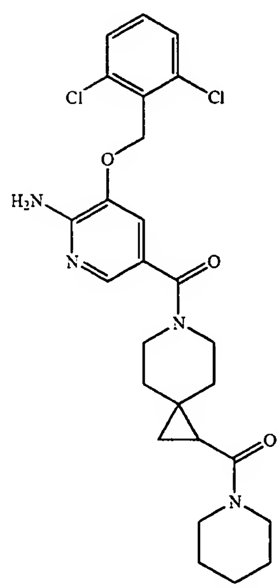

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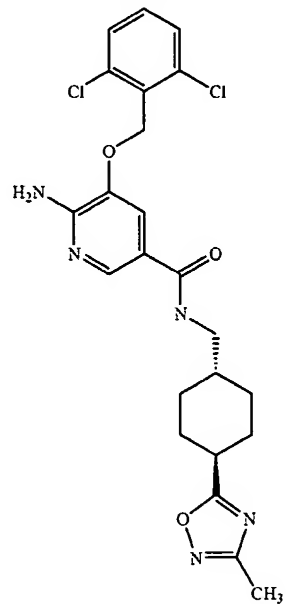
TABLE 6-continued



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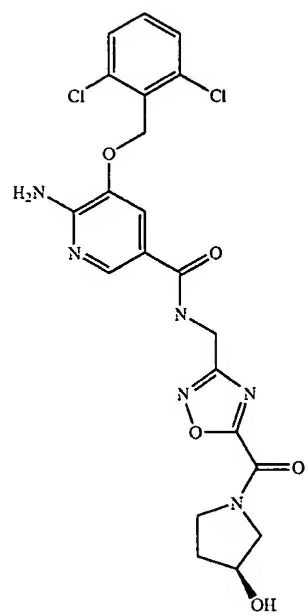

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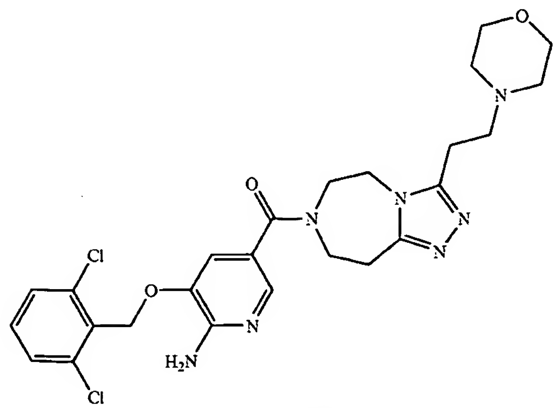
TABLE 6-continued



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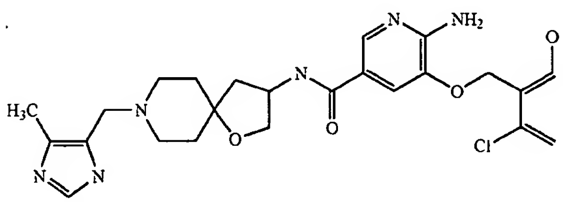

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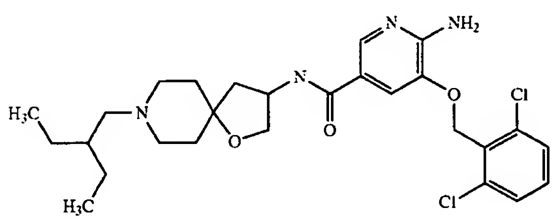
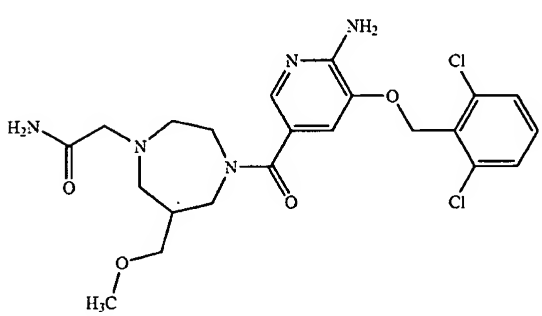


% Inhibition = 74



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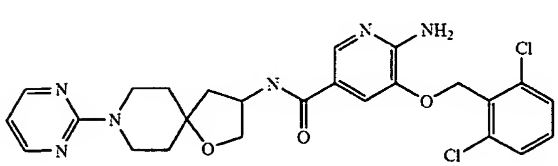

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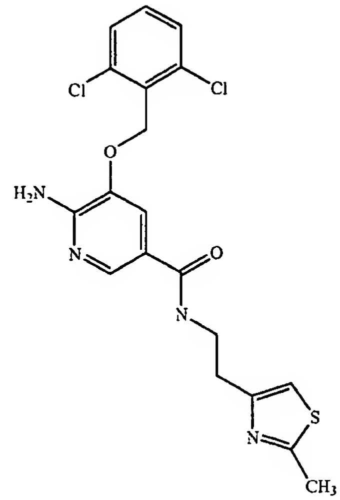
TABLE 6-continued



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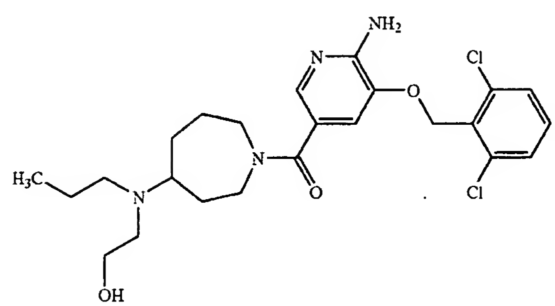

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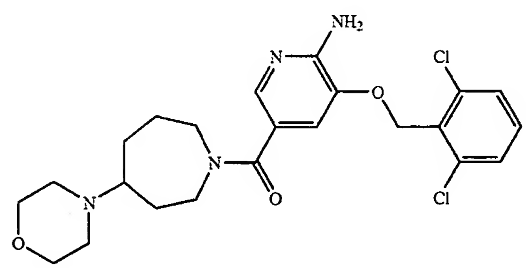

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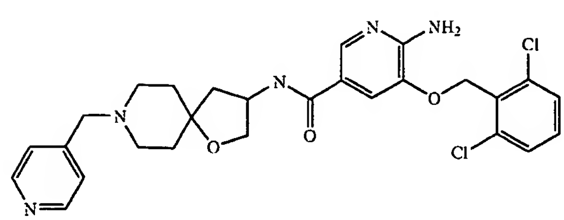

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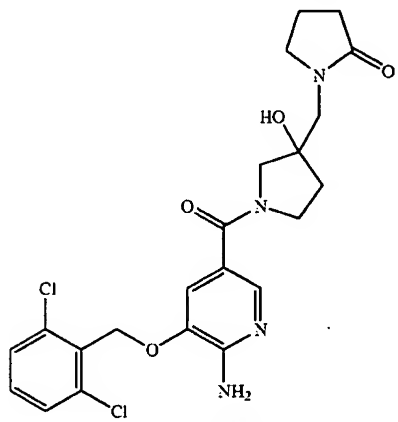
TABLE 6-continued

Section K: Examples L-337 to L-352



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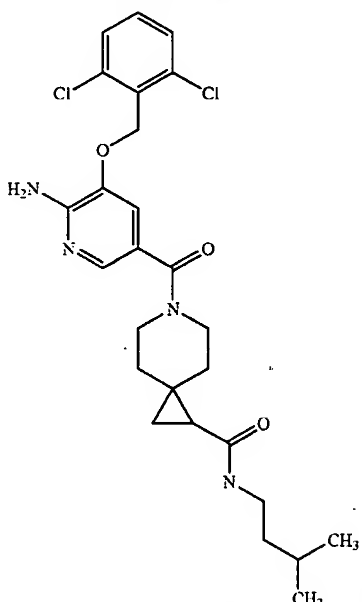

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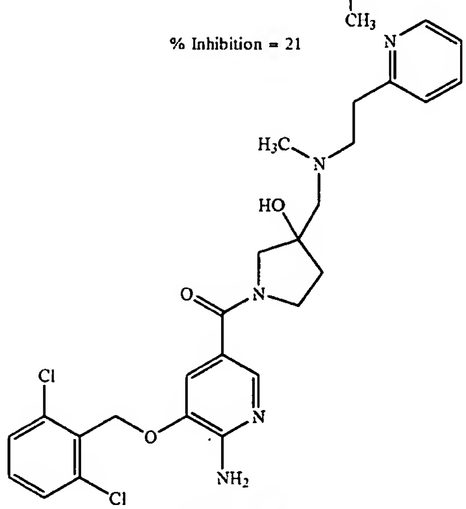

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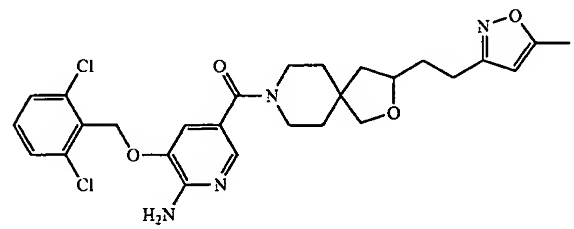
TABLE 6-continued



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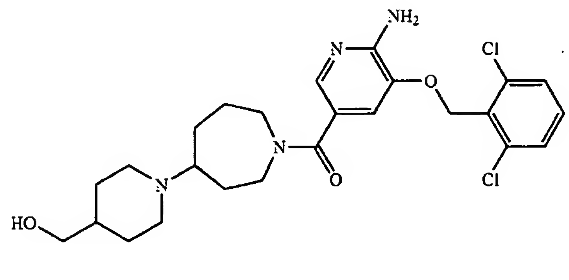

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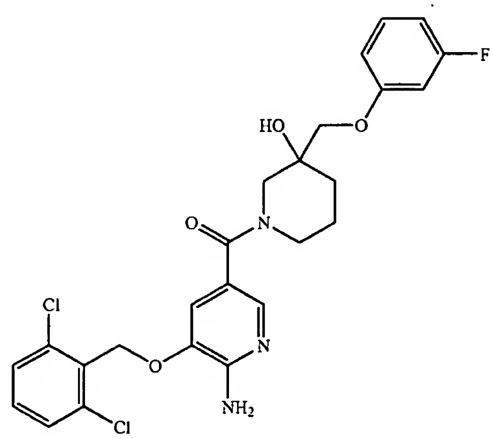

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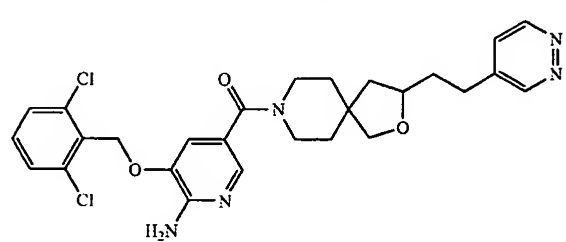

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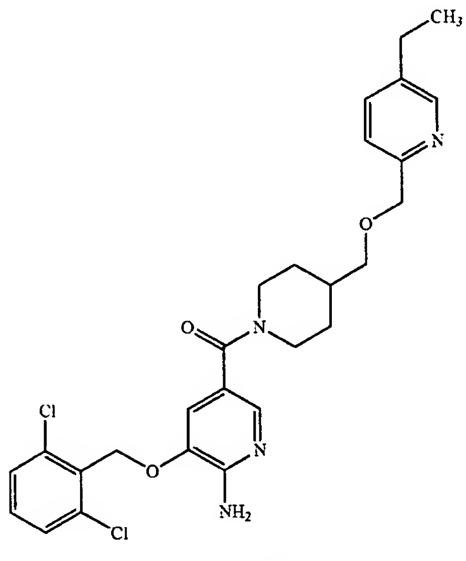
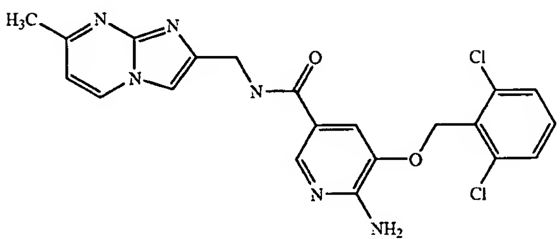
TABLE 6-continued



% Inhibition = 41



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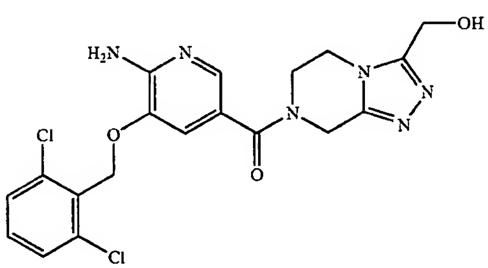

% Inhibition = 31

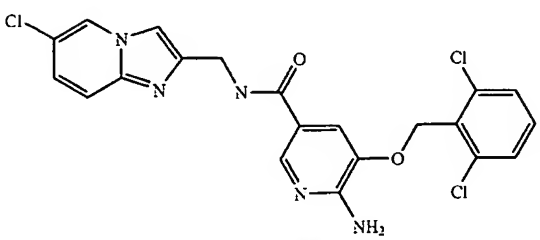

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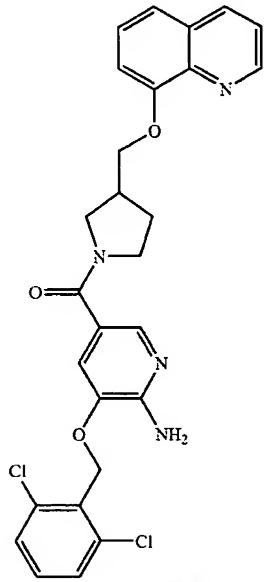
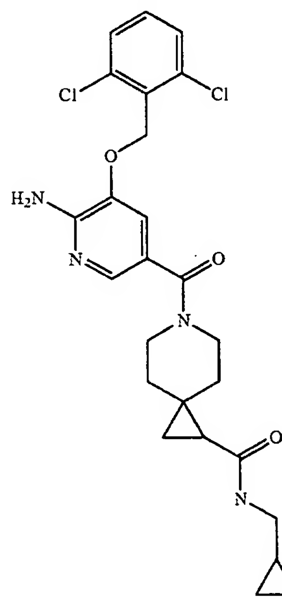
TABLE 6-continued



% Inhibition = 35



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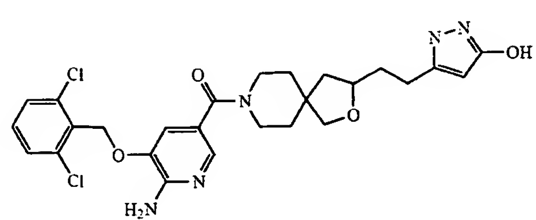

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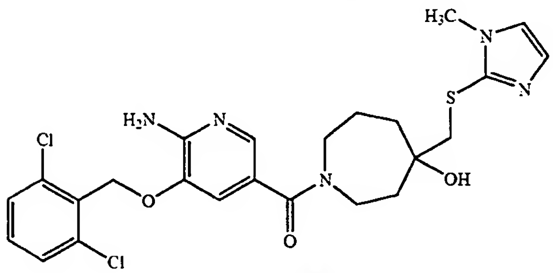
TABLE 6-continued



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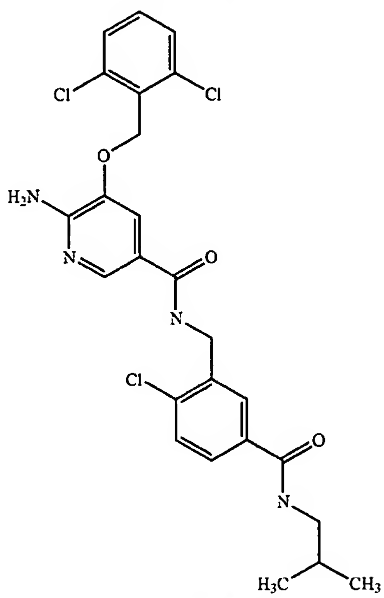

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TABLE 7

Section A: Examples L-353 to L-368

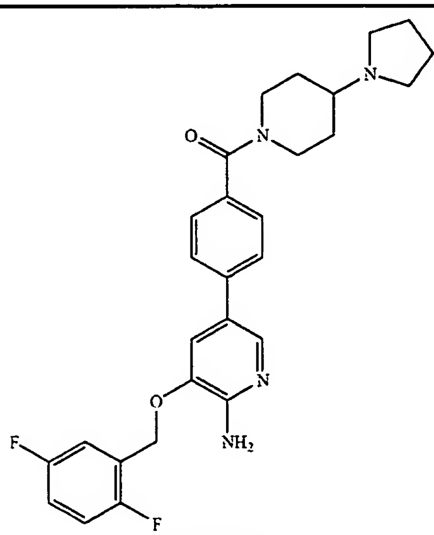

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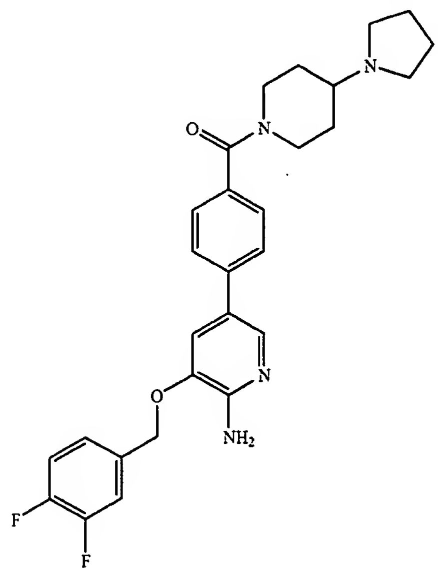
TABLE 7-continued



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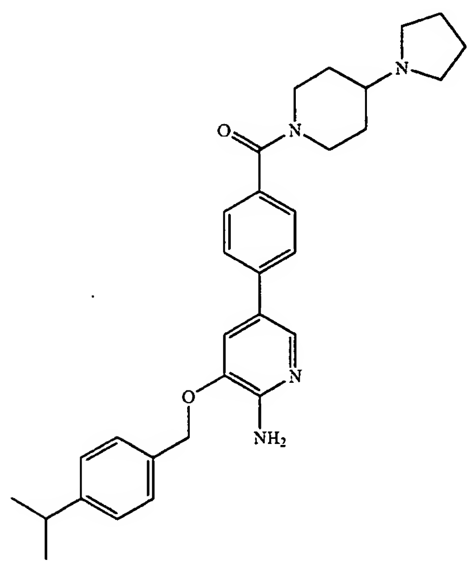

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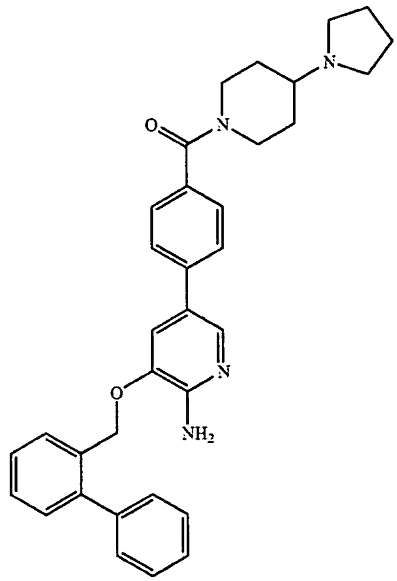
TABLE 7-continued



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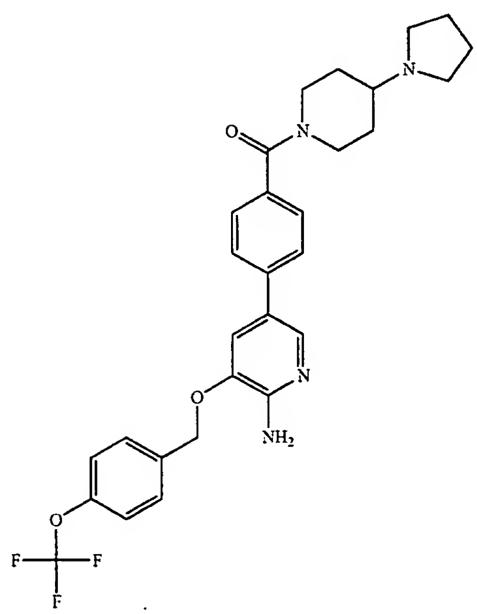

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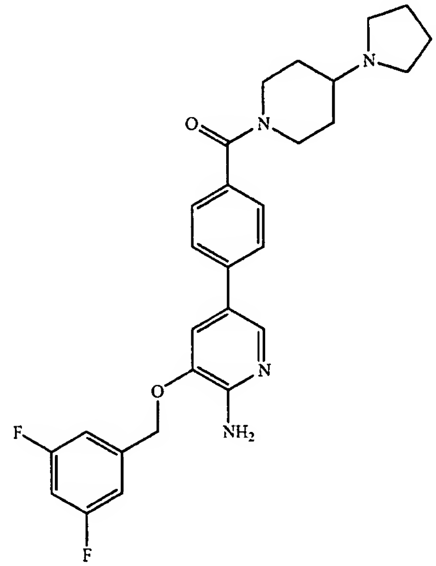
TABLE 7-continued



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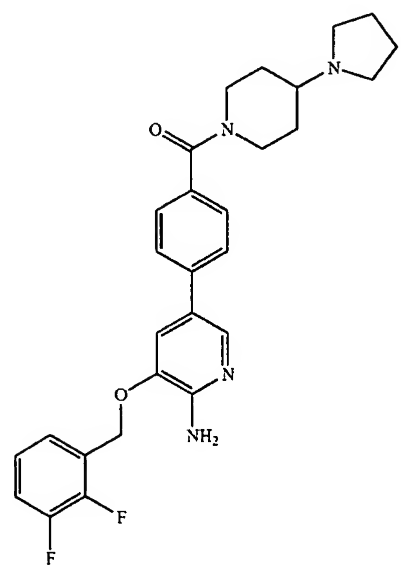

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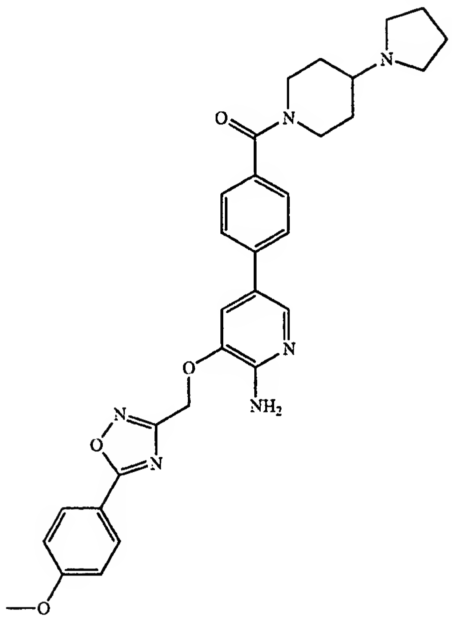
TABLE 7-continued



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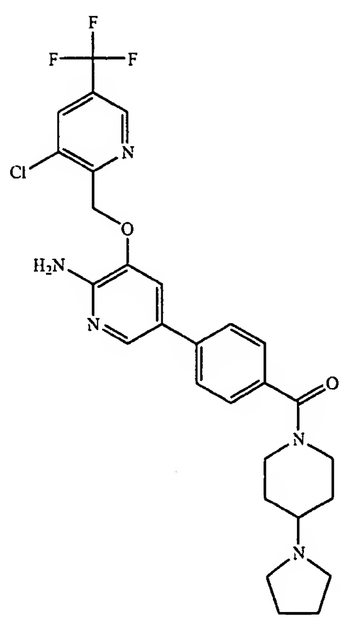
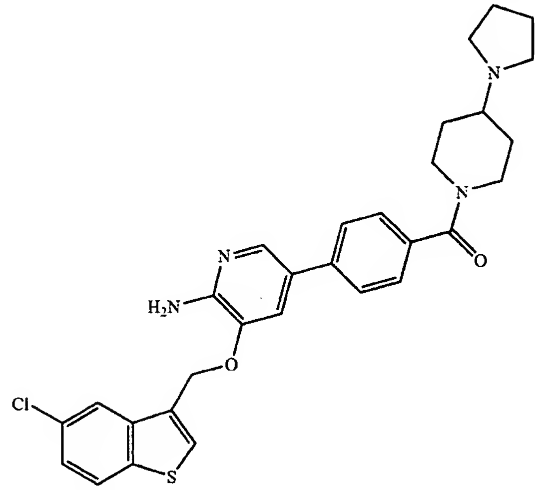


% Inhibition = 8

TABLE 7-continued



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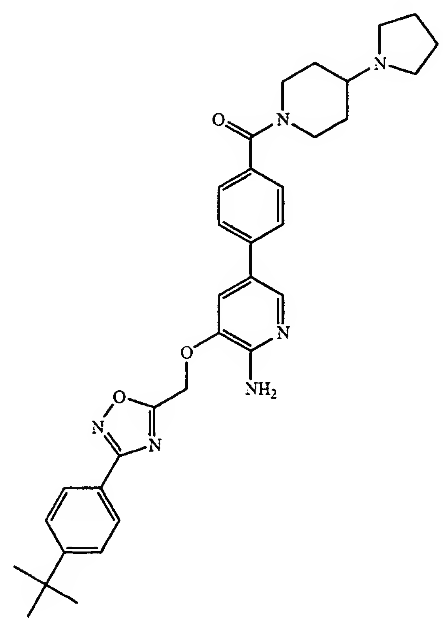
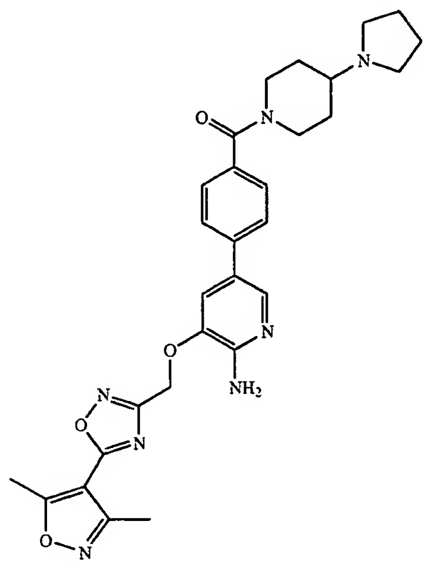


% Inhibition = 36

TABLE 7-continued



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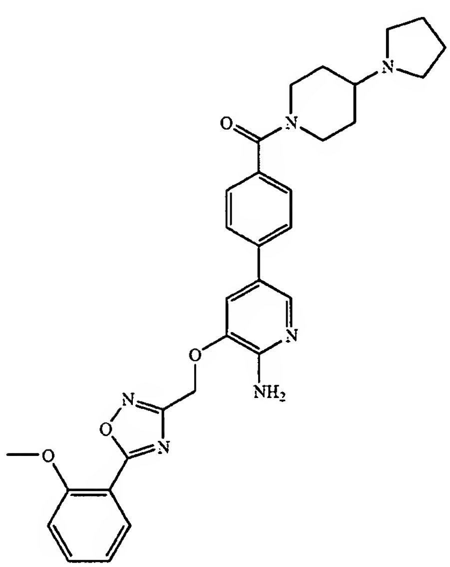

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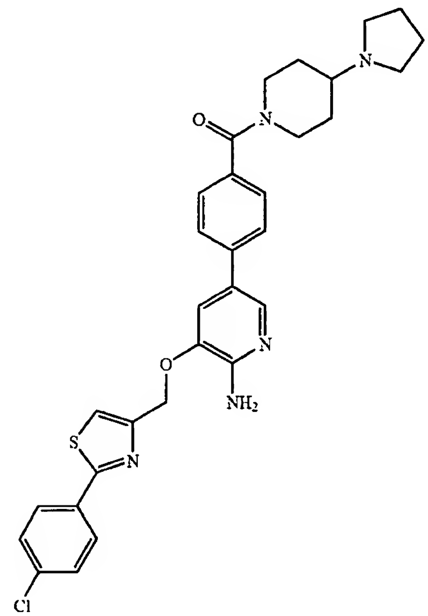
TABLE 7-continued



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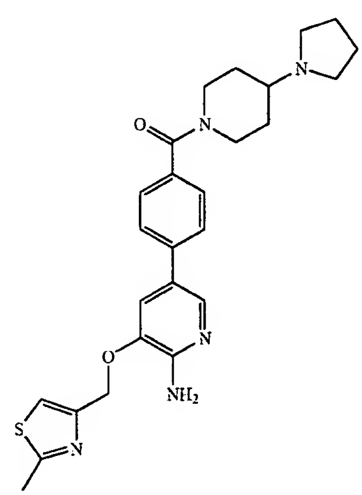

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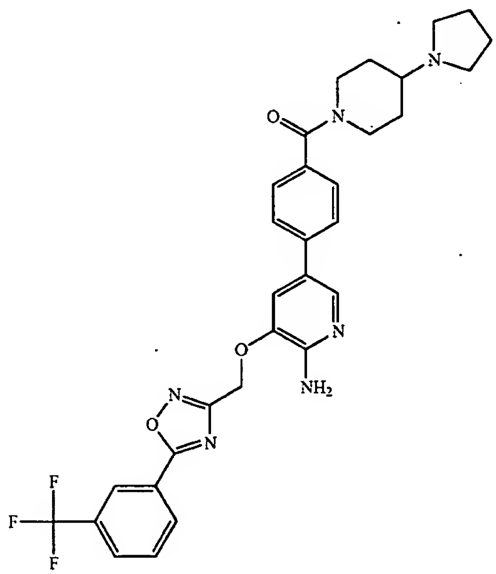

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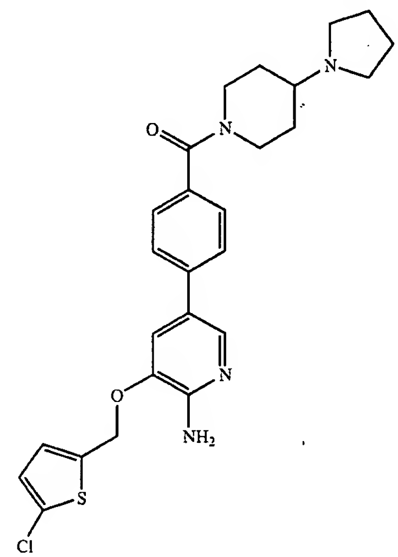

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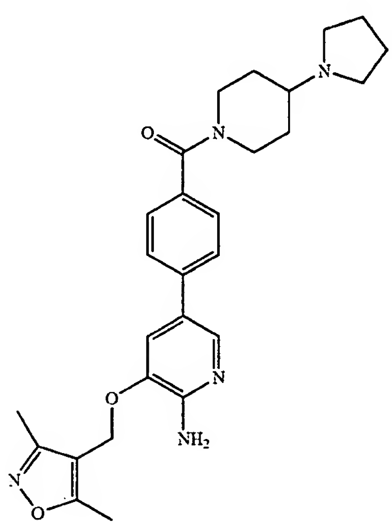
Section B: Examples L-369 to L-384



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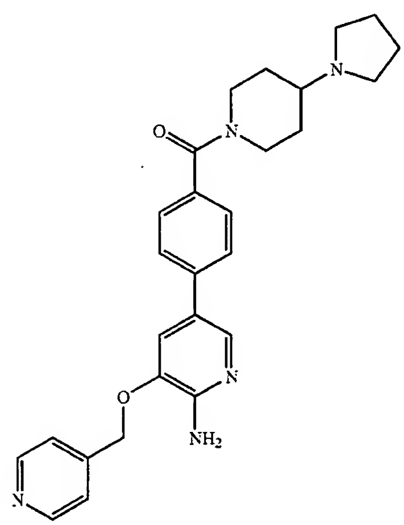

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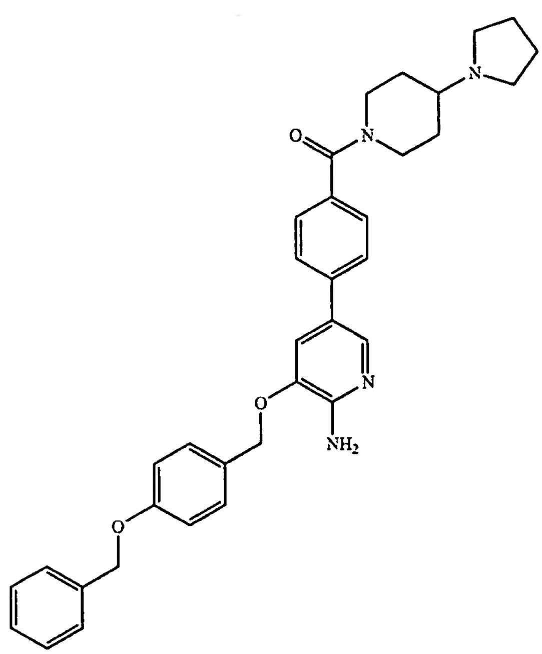

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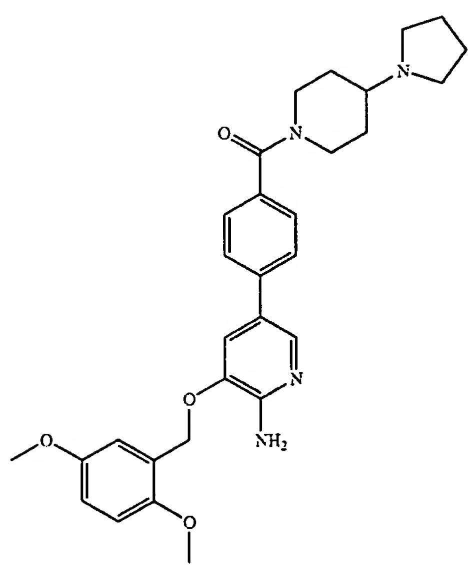

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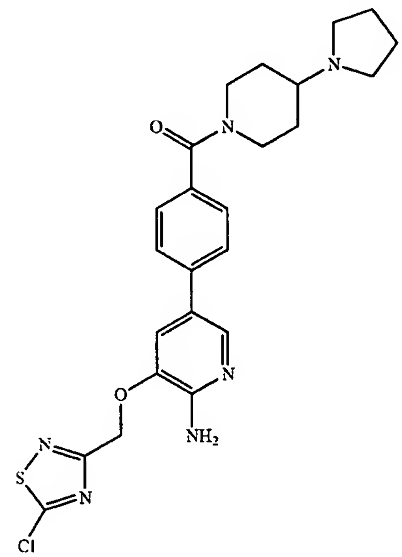
TABLE 7-continued



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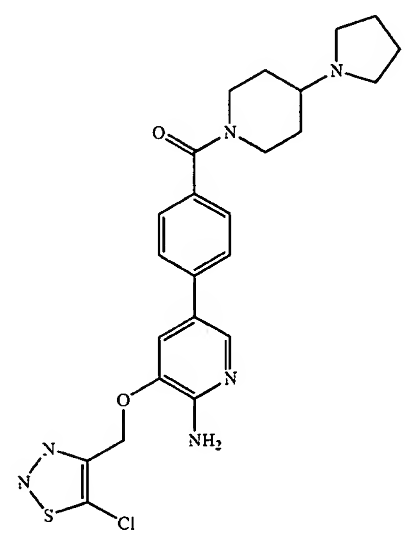

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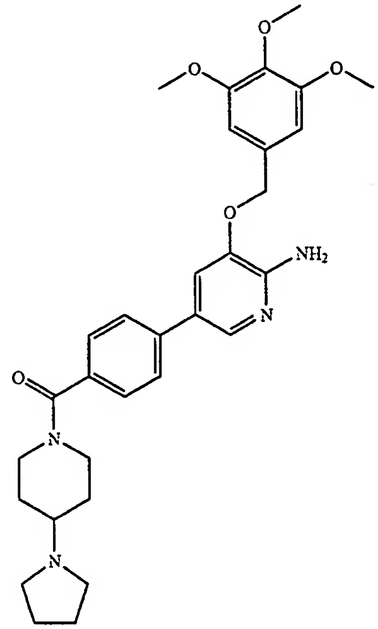
TABLE 7-continued



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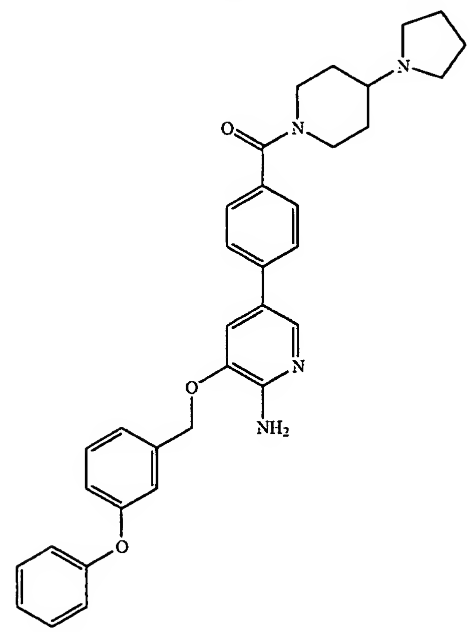

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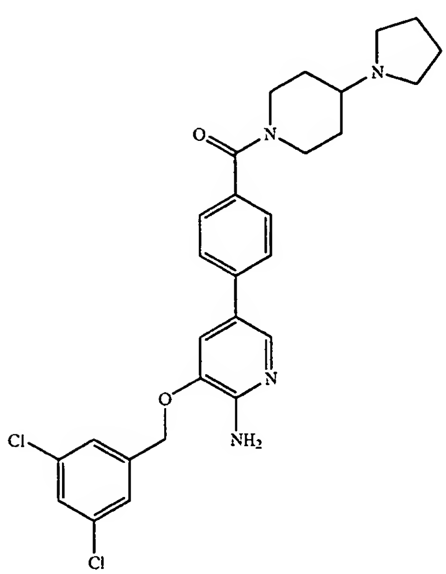

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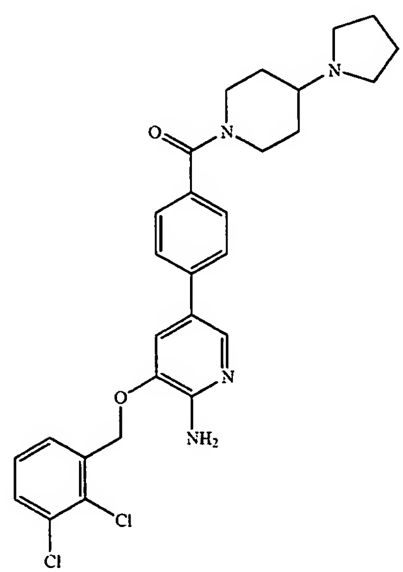

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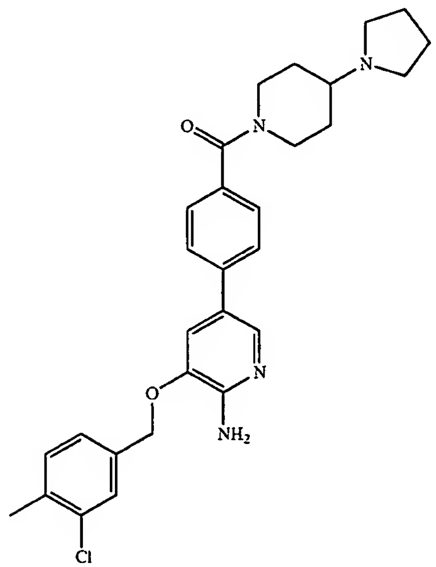
TABLE 7-continued



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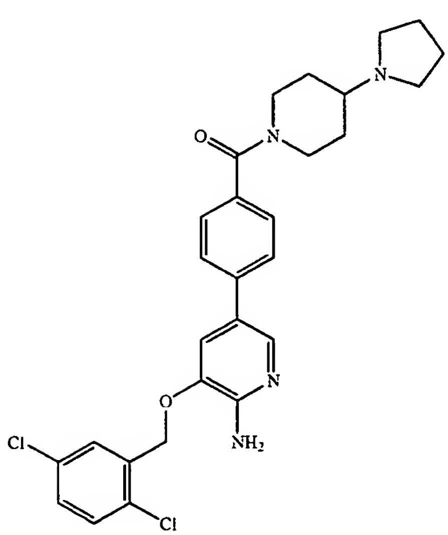

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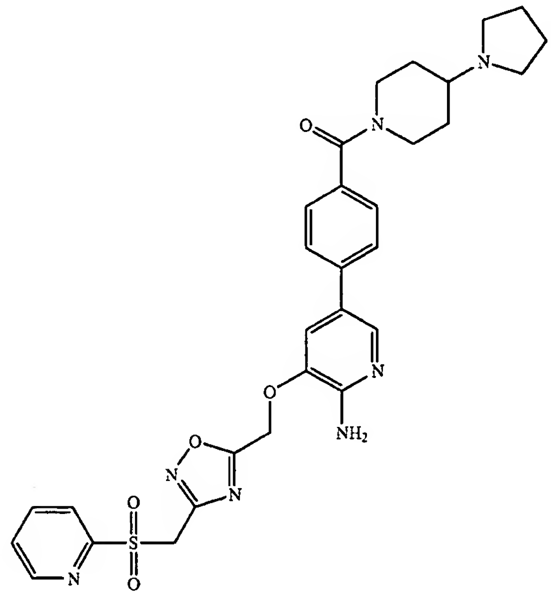
TABLE 7-continued



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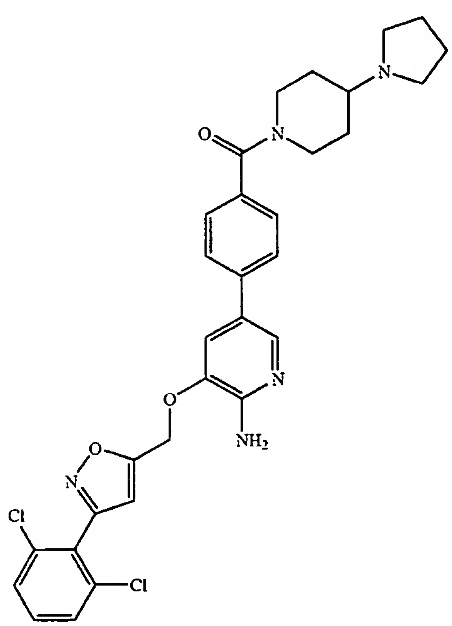

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TABLE 7-continued

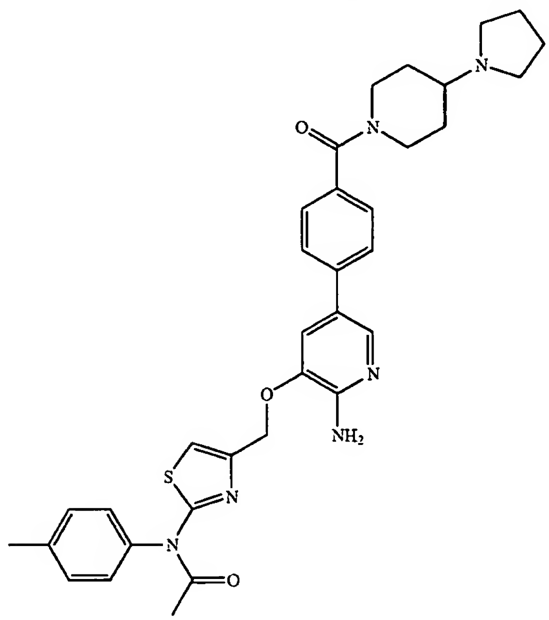

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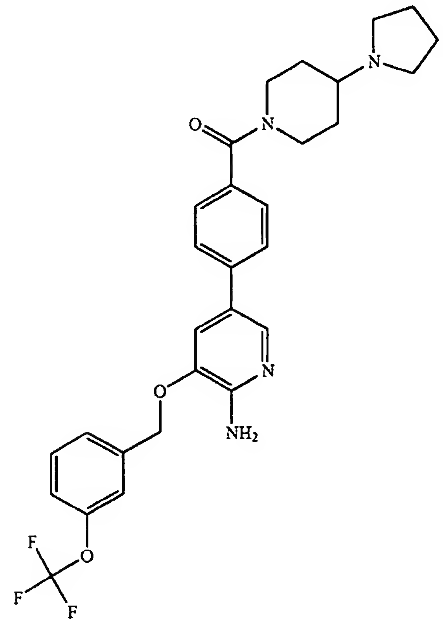
TABLE 7-continued



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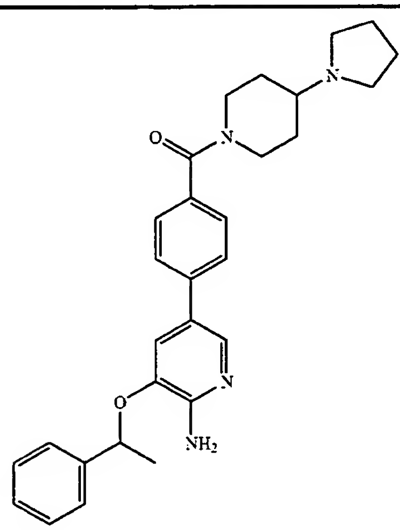
Section C: Examples L-385 to L-400



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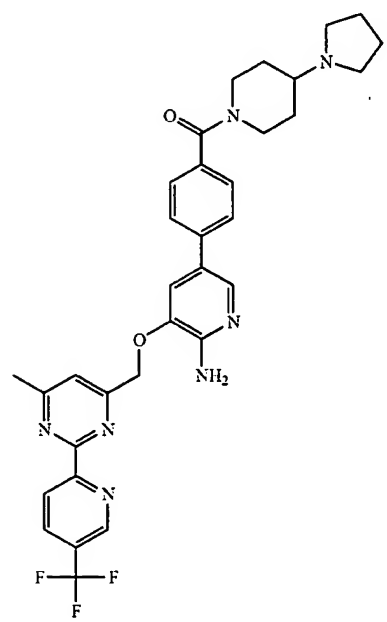

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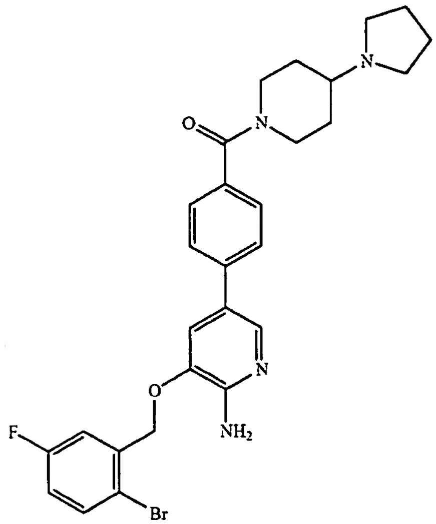

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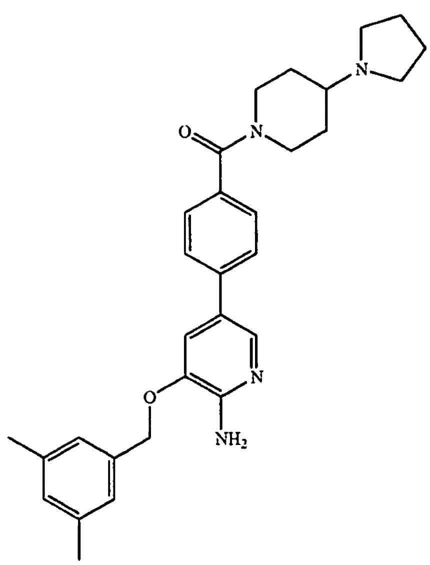

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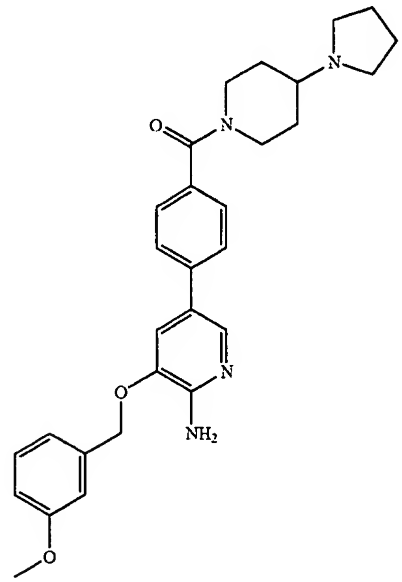
TABLE 7-continued



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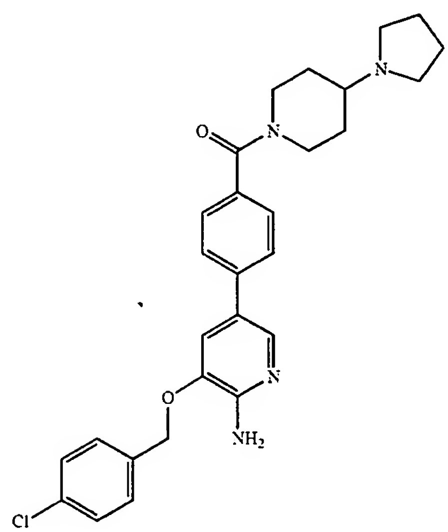

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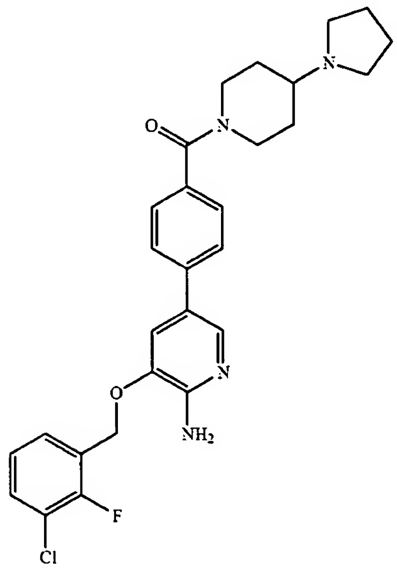

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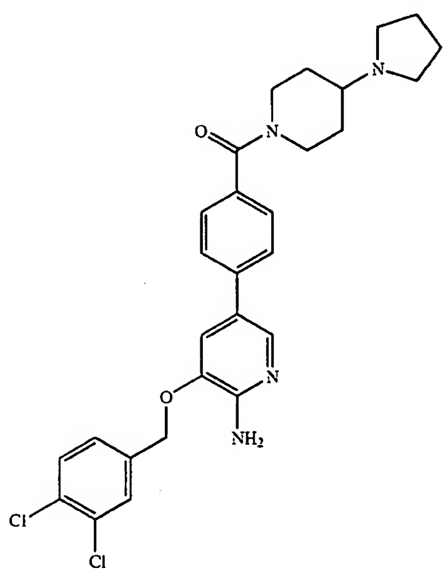

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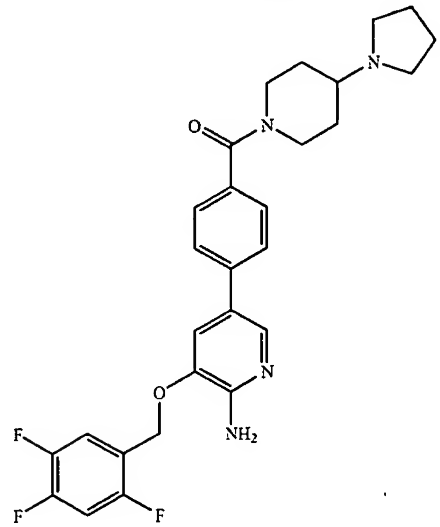
TABLE 7-continued



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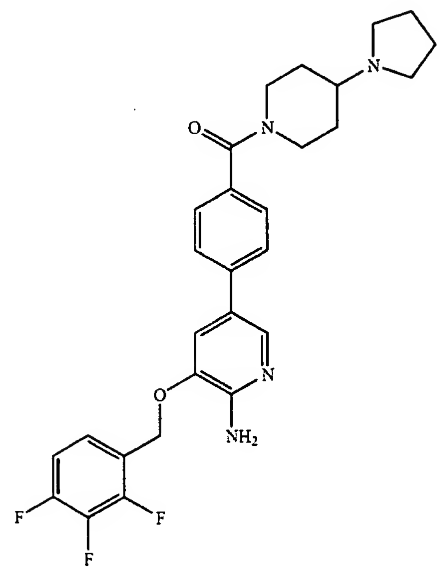

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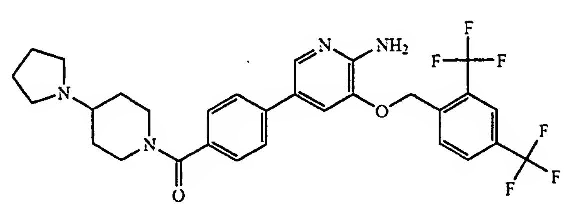

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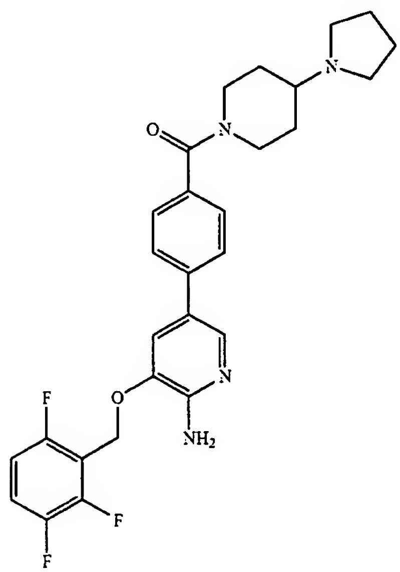

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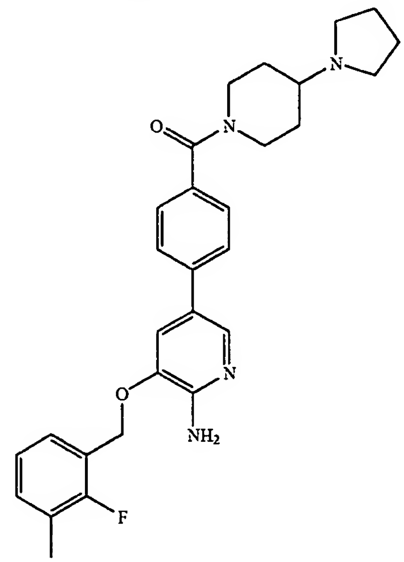

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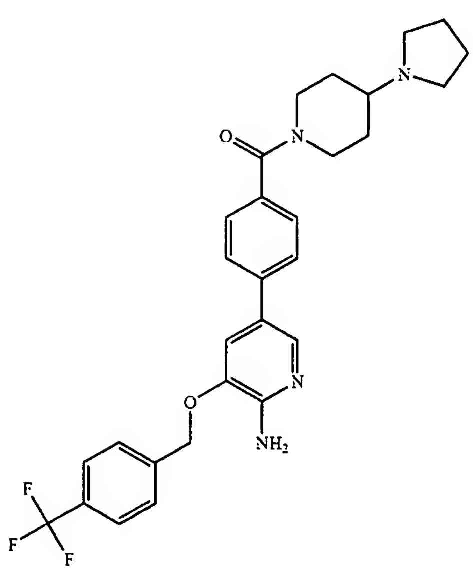

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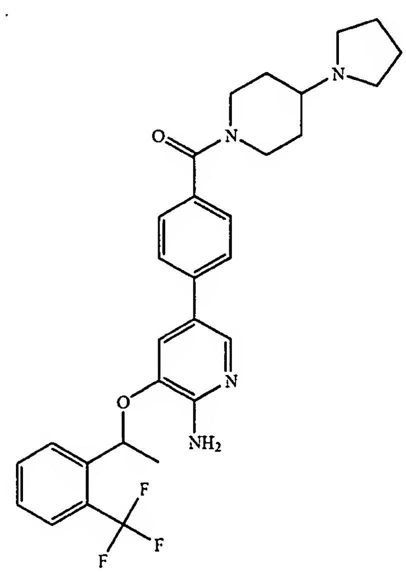

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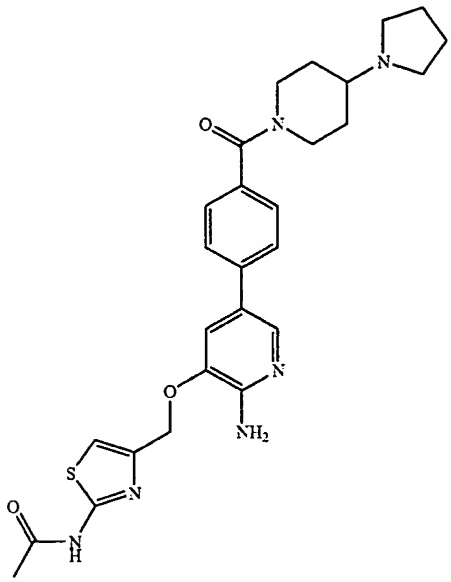
TABLE 7-continued

Section D: Examples L-401 to L-416



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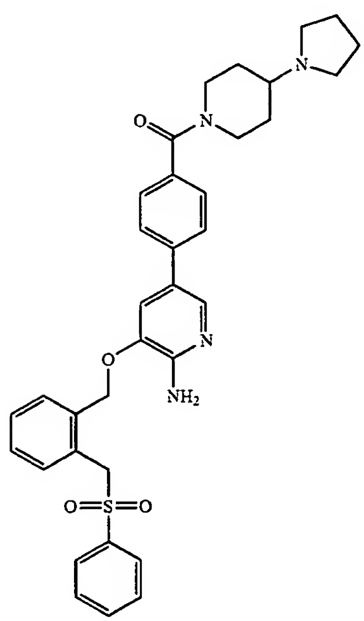

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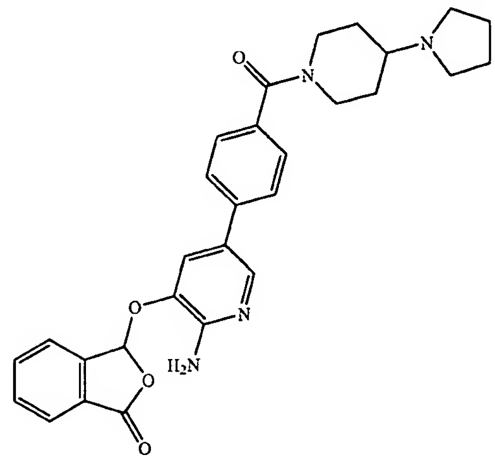
TABLE 7-continued



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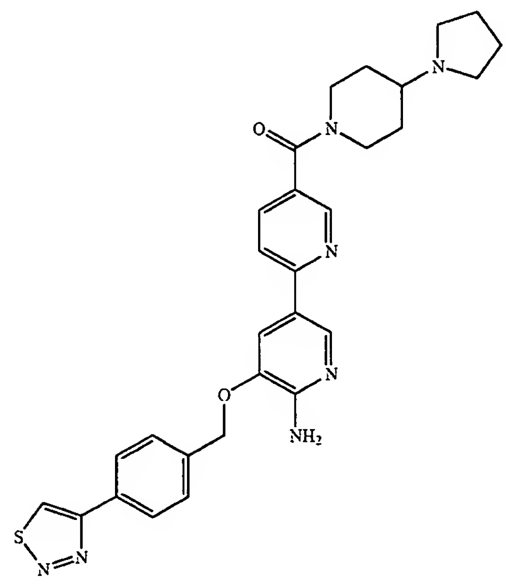
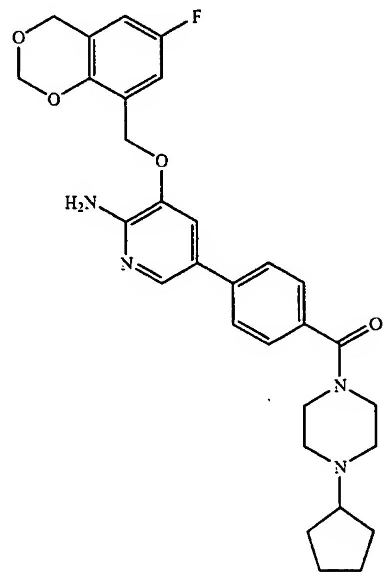


% Inhibition = 41

TABLE 7-continued



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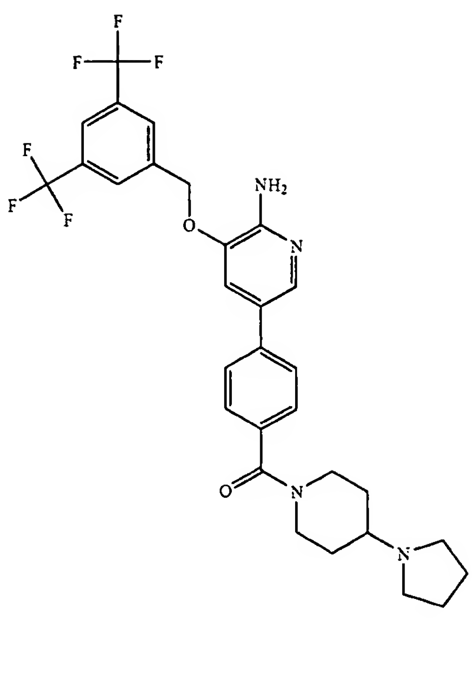

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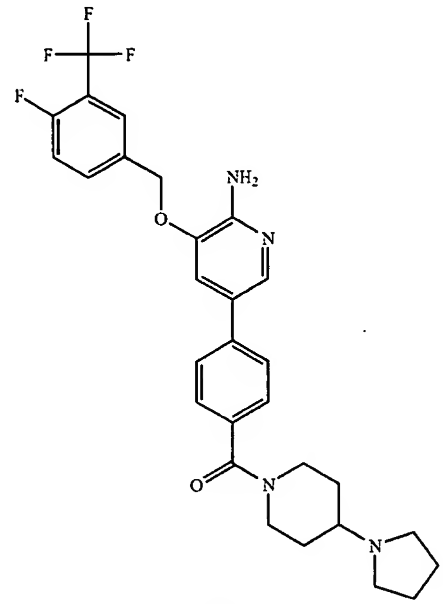
TABLE 7-continued



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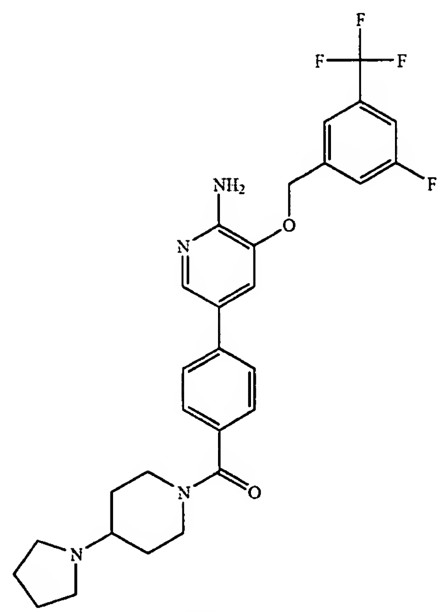

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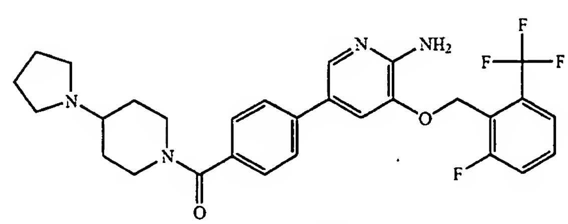

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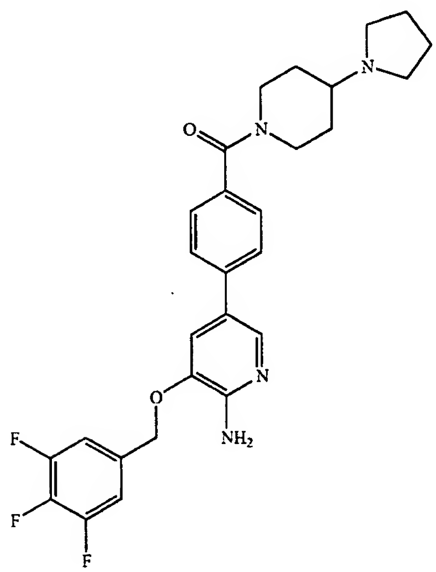
TABLE 7-continued



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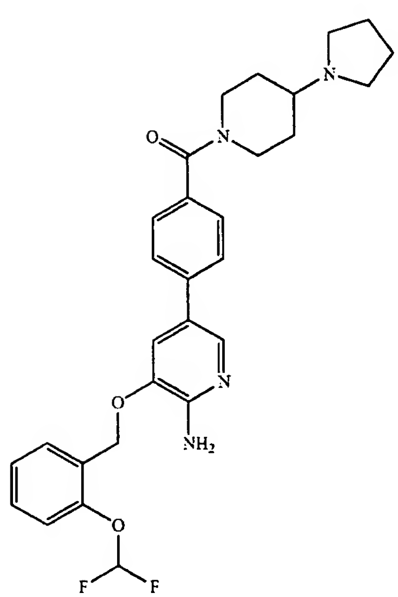

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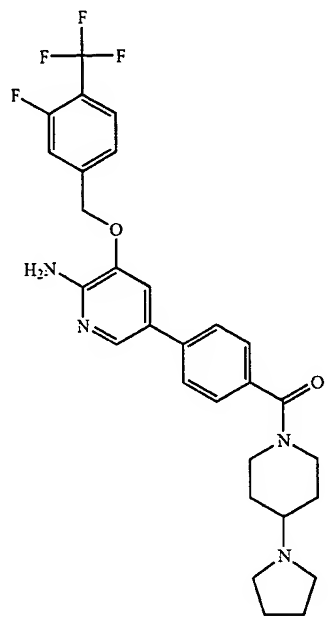
TABLE 7-continued



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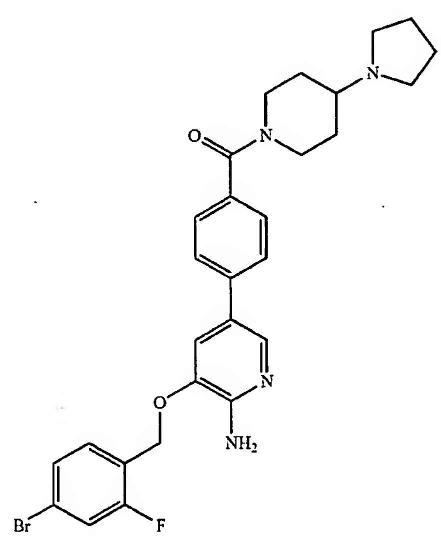

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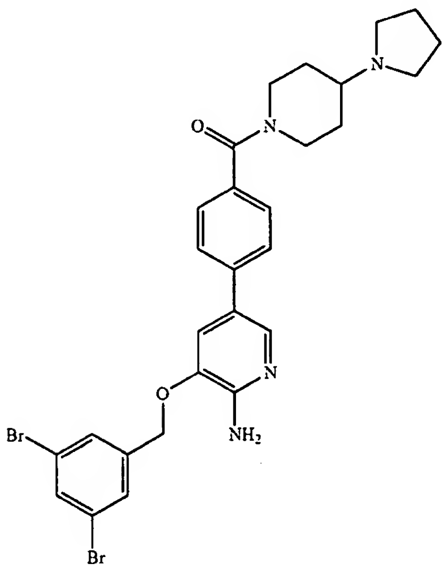
TABLE 7-continued



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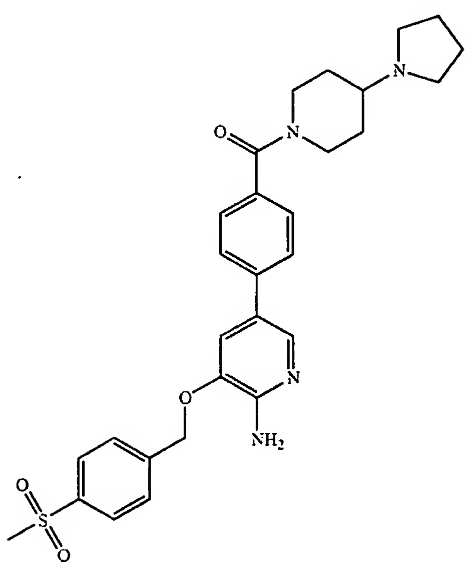

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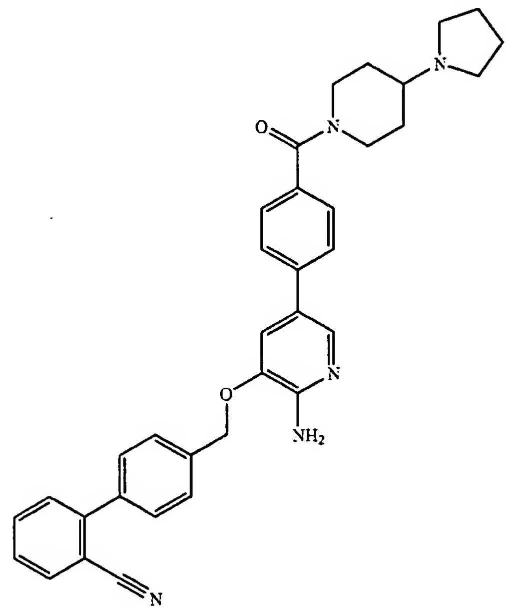
TABLE 7-continued



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Section E: Examples L-417 to L-432

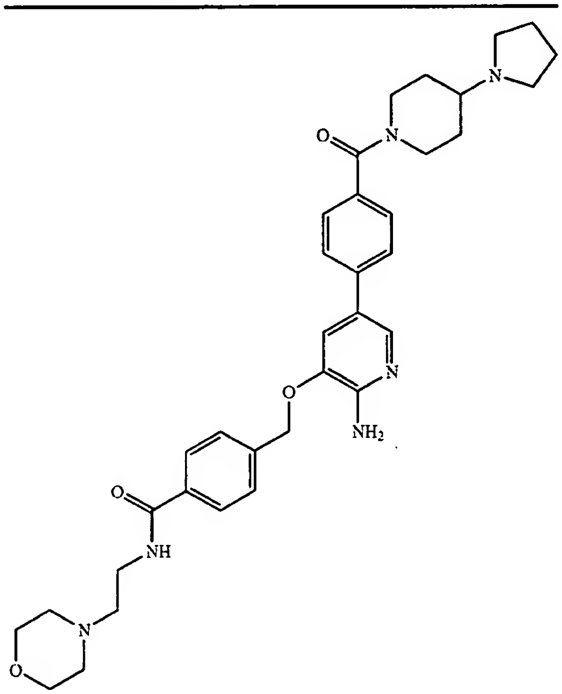

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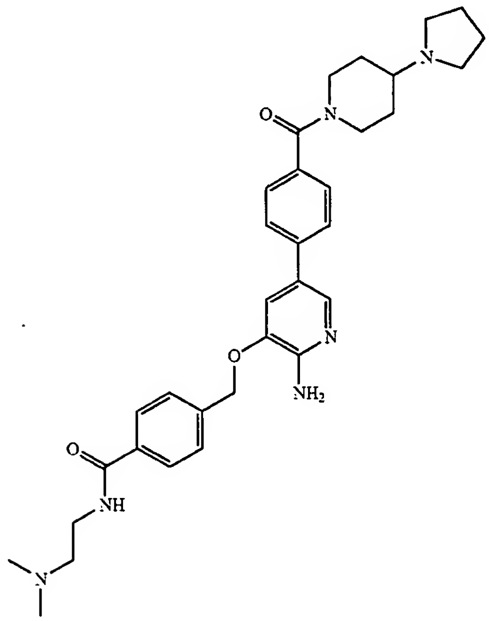
TABLE 7-continued



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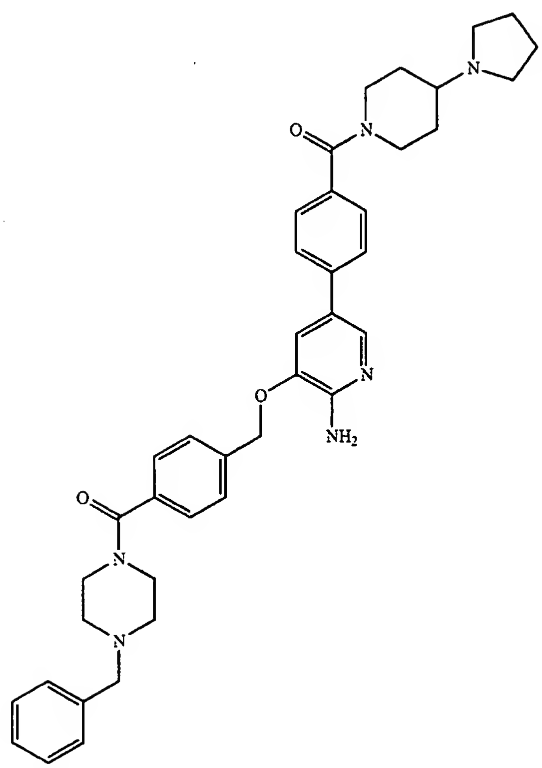

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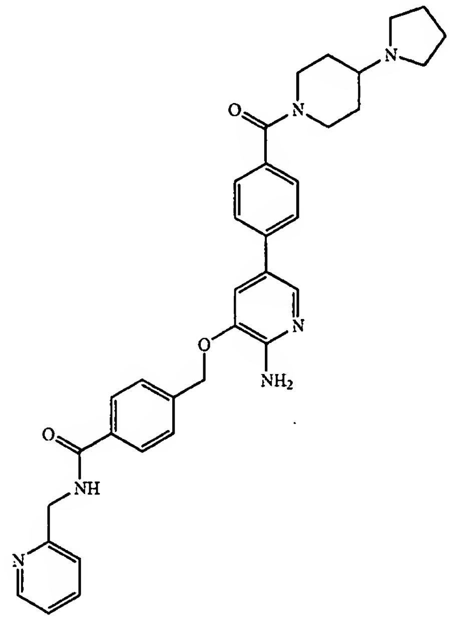
TABLE 7-continued



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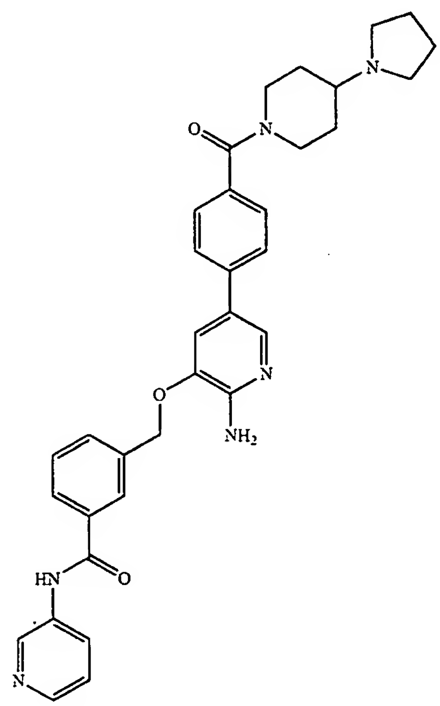

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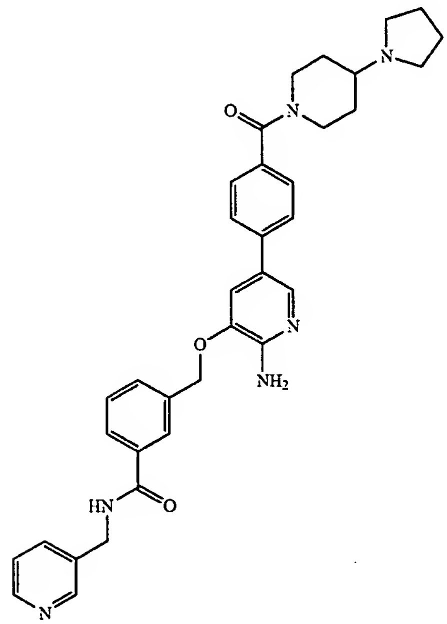

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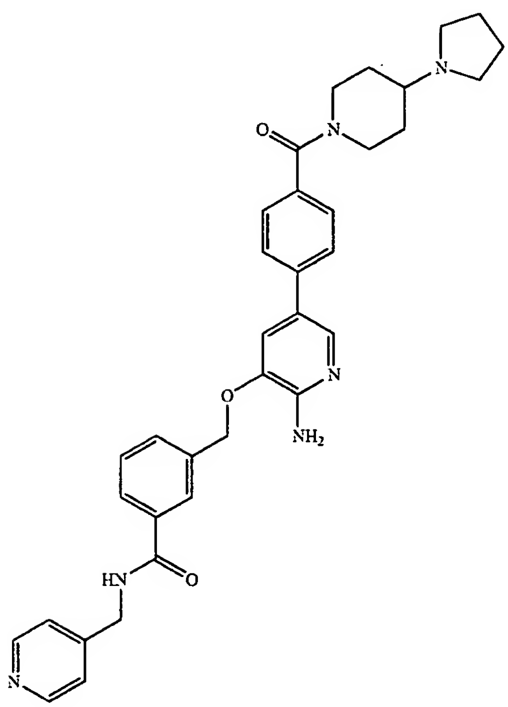

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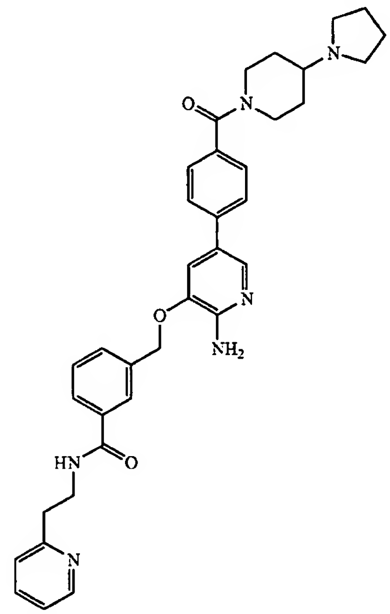
TABLE 7-continued



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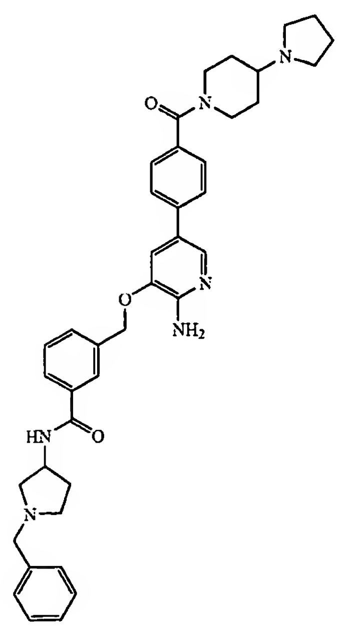

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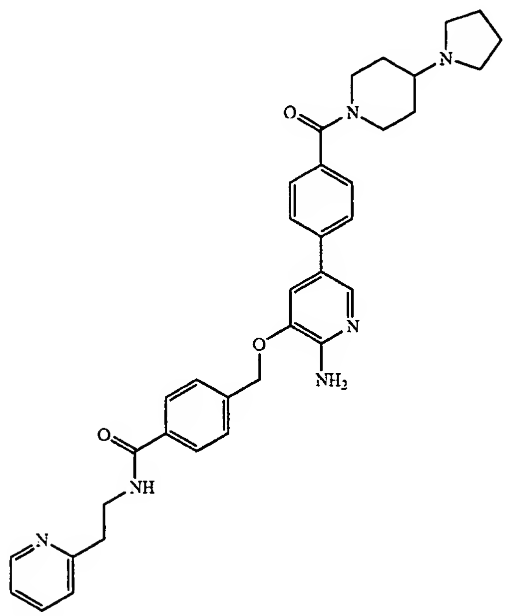
TABLE 7-continued



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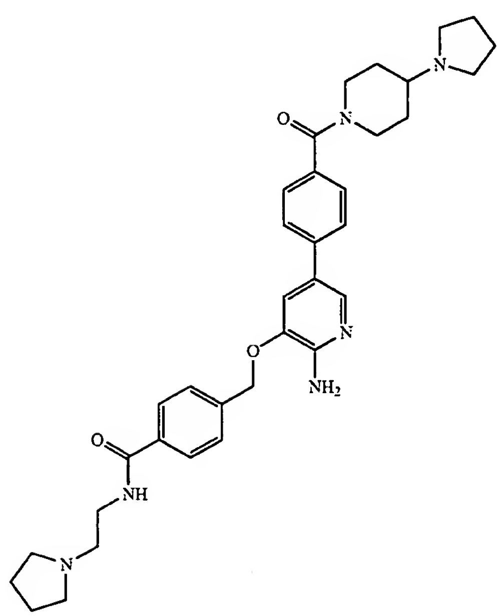

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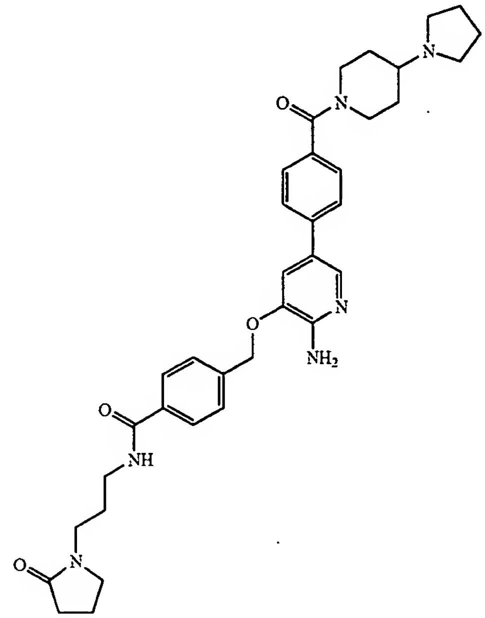

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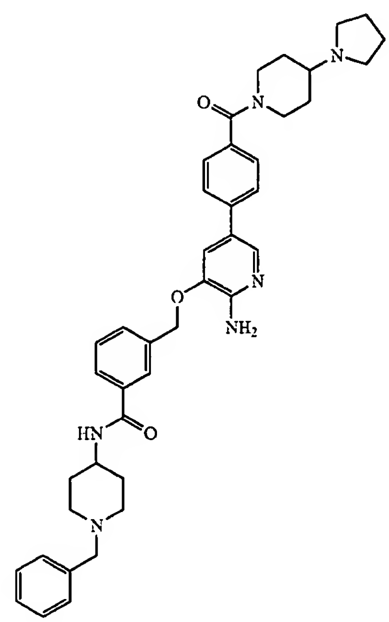

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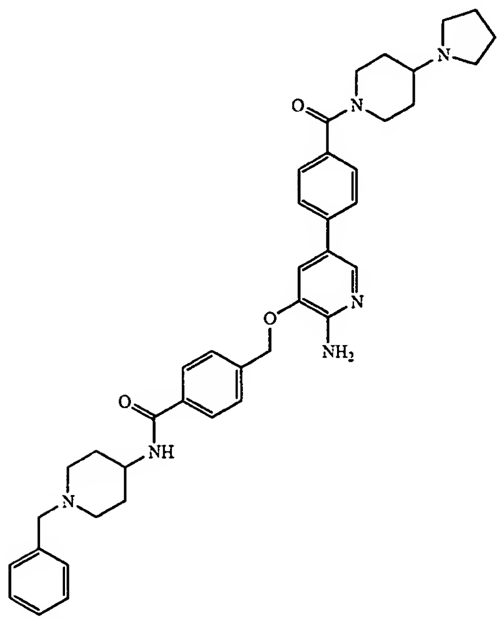
TABLE 7-continued



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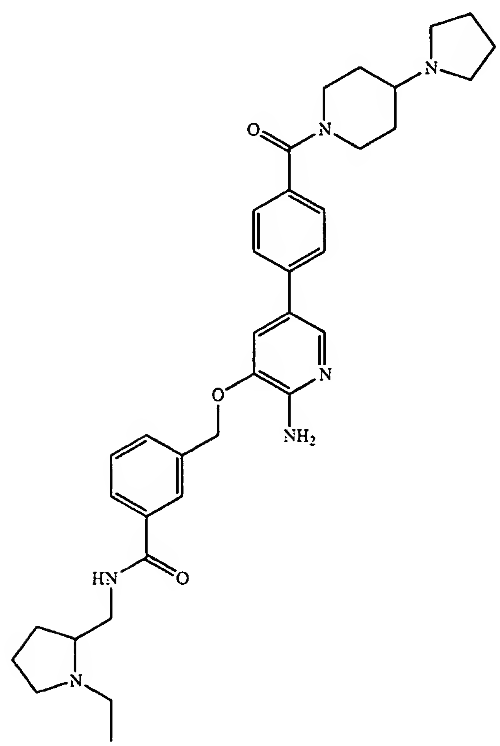

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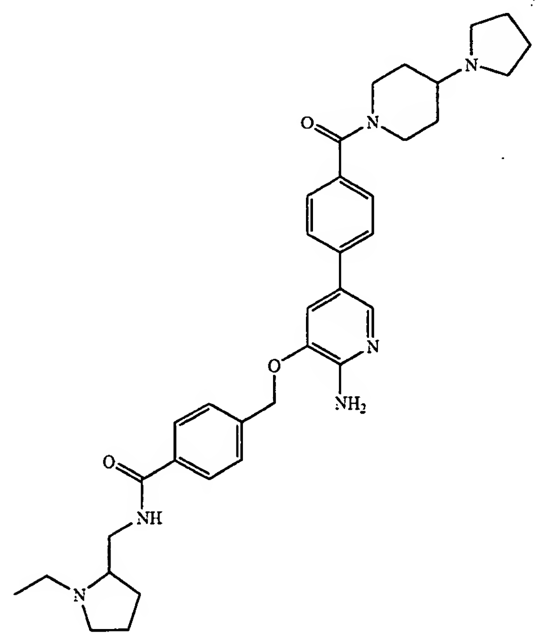
TABLE 7-continued



% Inhibition = 18

Section F: Examples L-433 to L-448

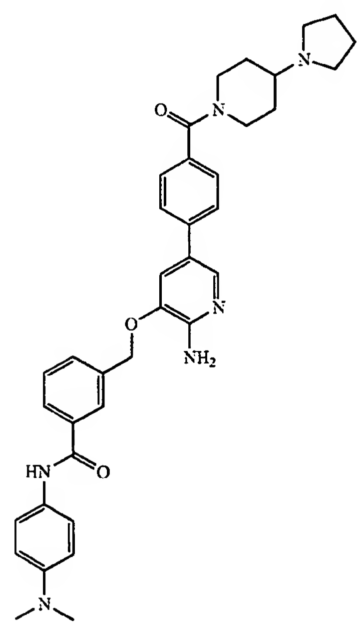


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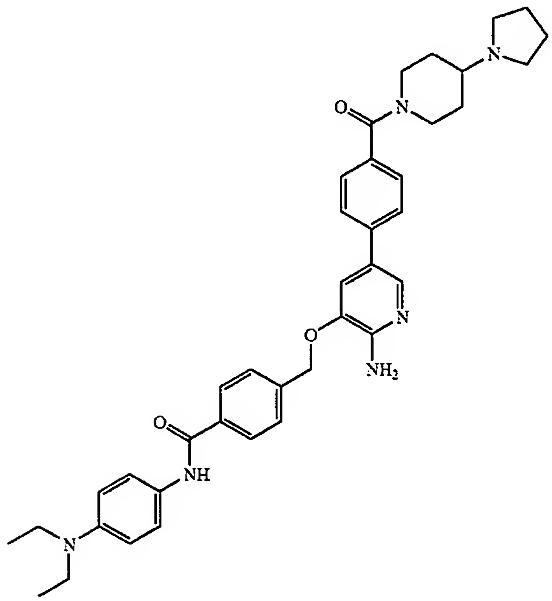
TABLE 7-continued



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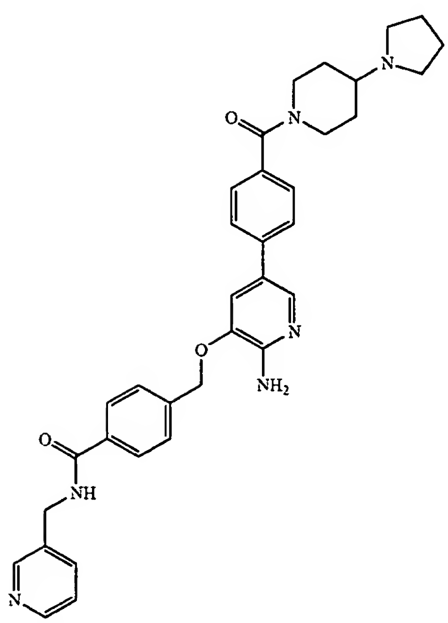
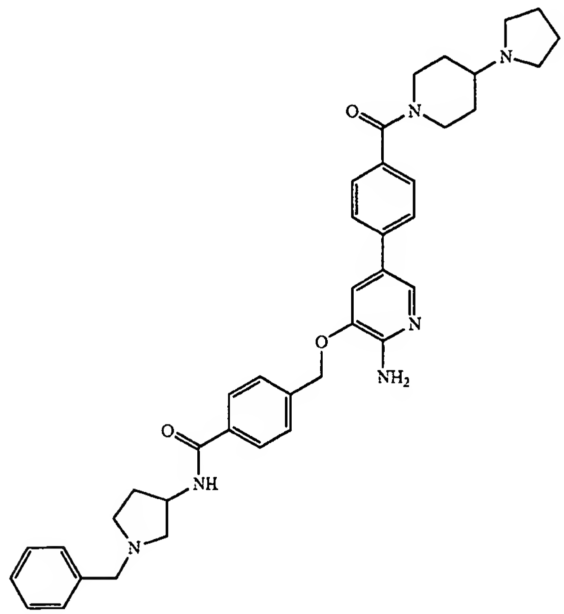


% Inhibition = 15

TABLE 7-continued



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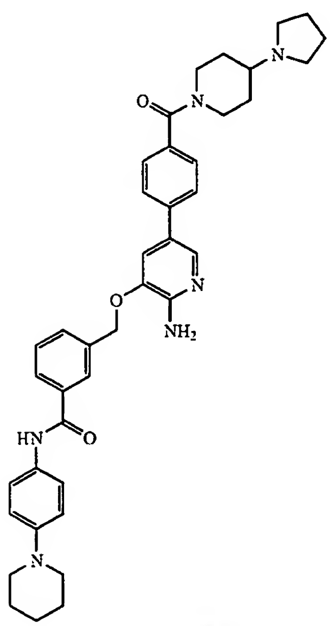

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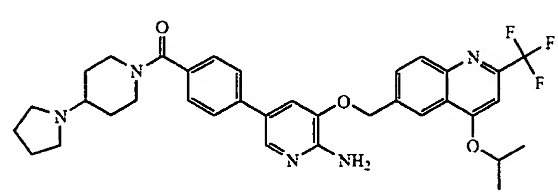
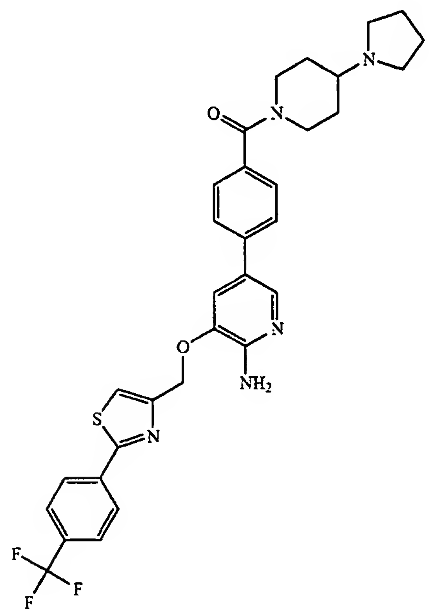
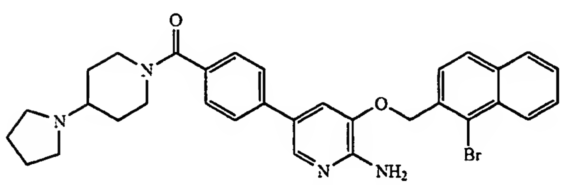


% Inhibition = 19

TABLE 7-continued



% Inhibition = 21



% Inhibition = 59

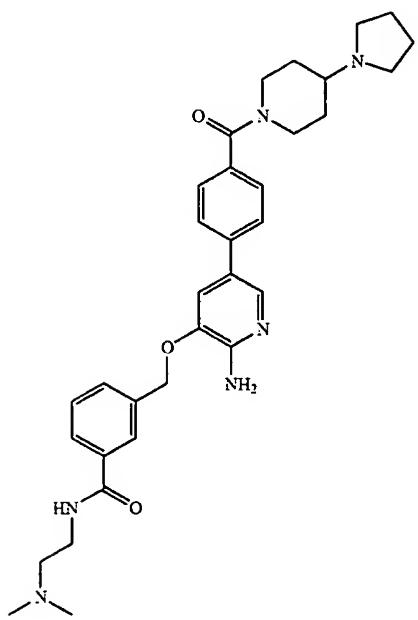


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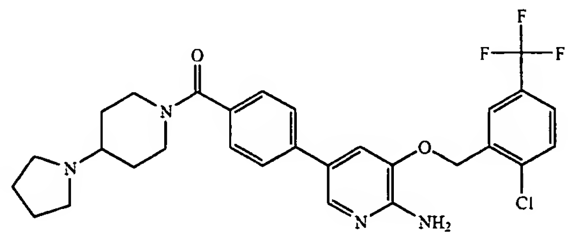
TABLE 7-continued



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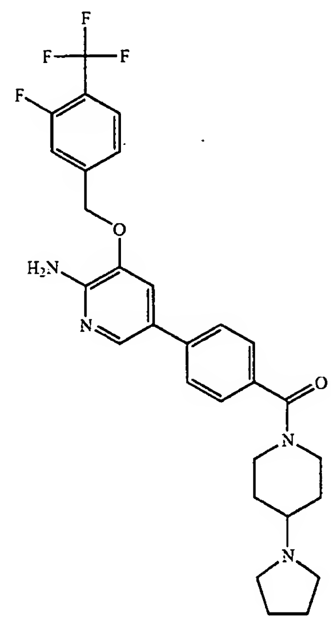

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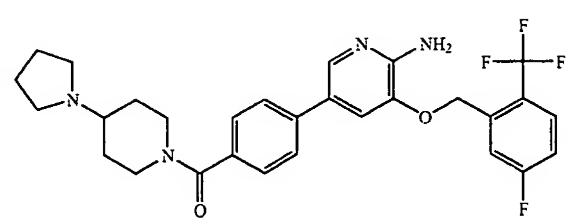
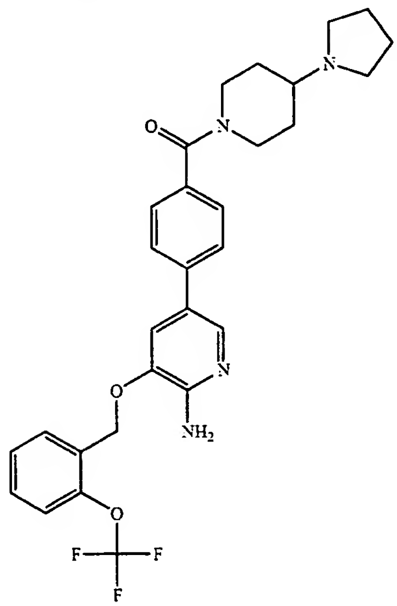


% Inhibition = 26

TABLE 7-continued



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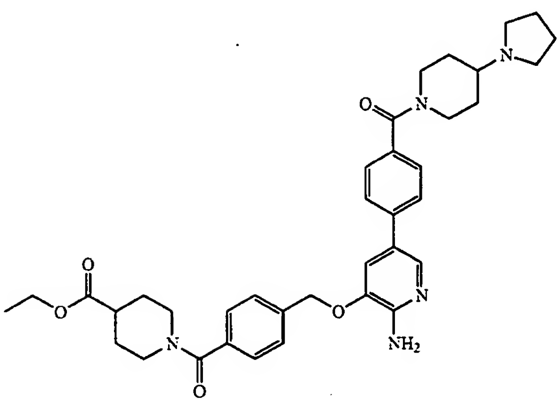

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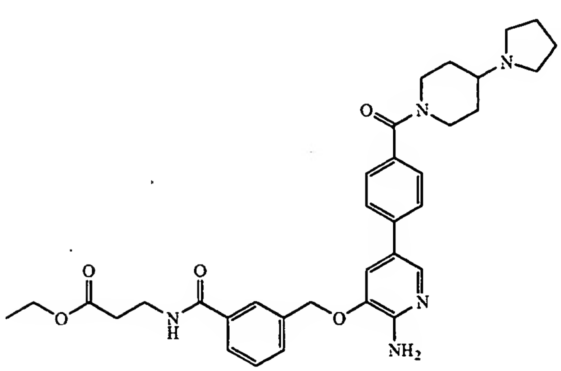

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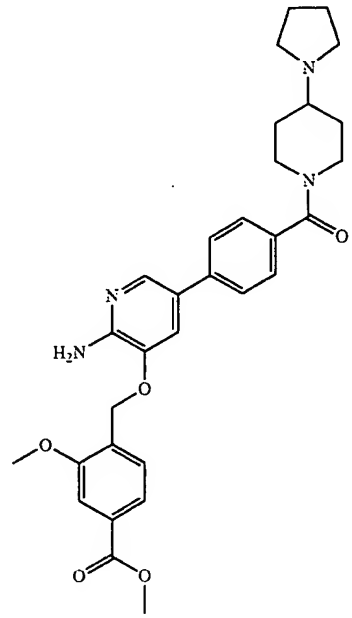
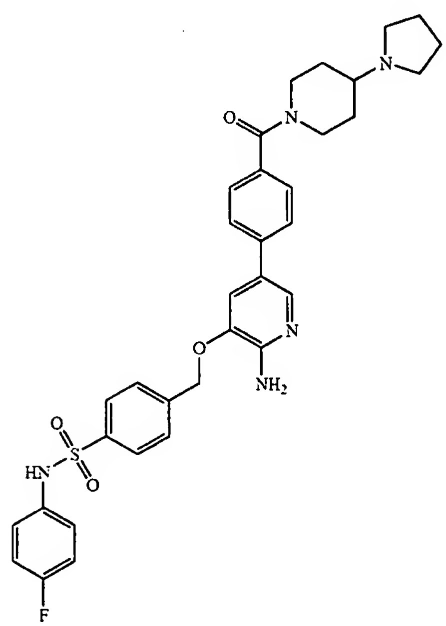
TABLE 7-continued



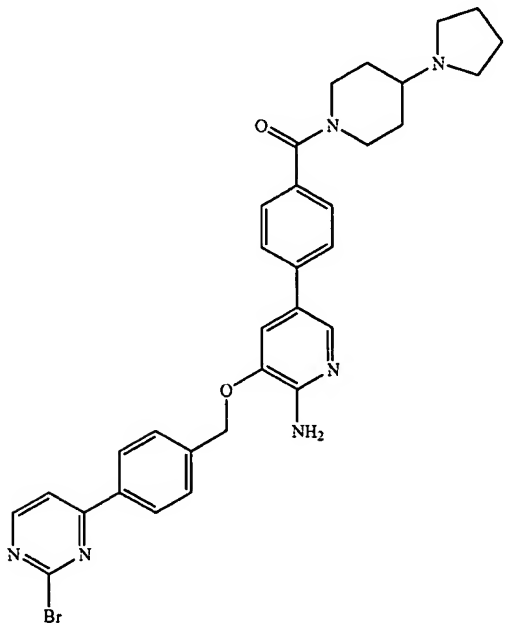
% Inhibition = 15

Section G: Examples L-449 to L-464



% Inhibition = 15

TABLE 7-continued



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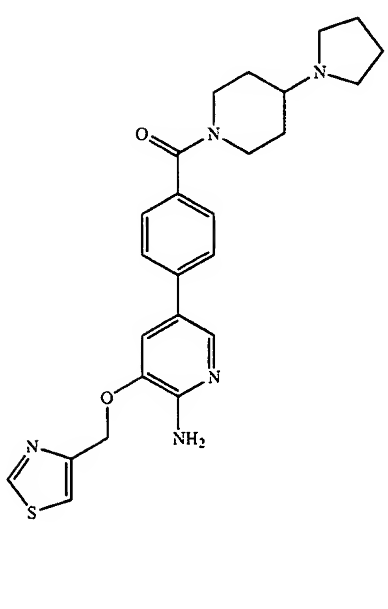

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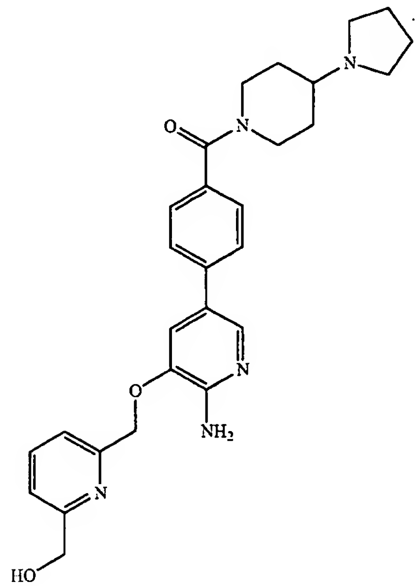

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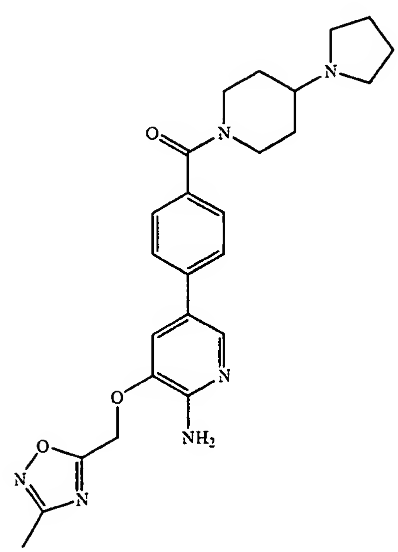
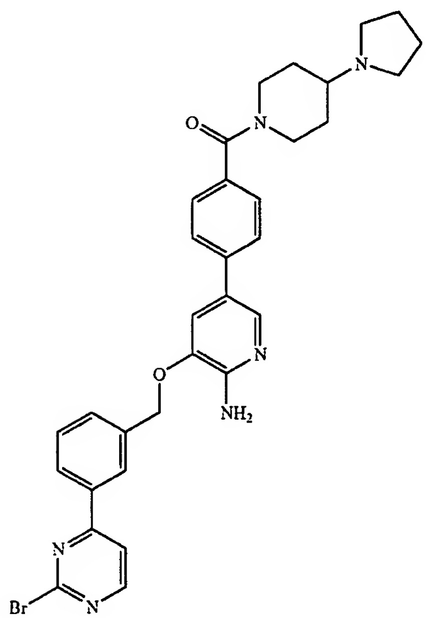


TABLE 7-continued



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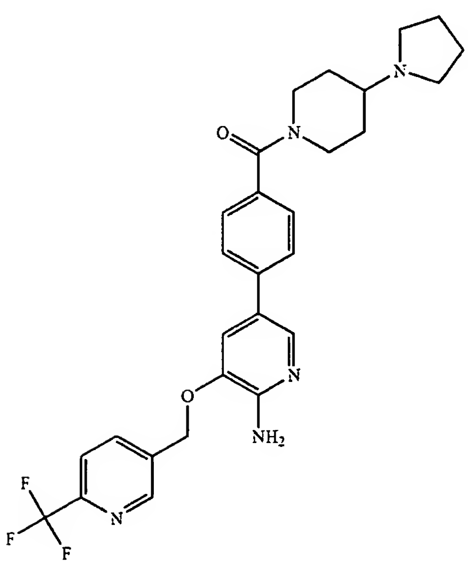

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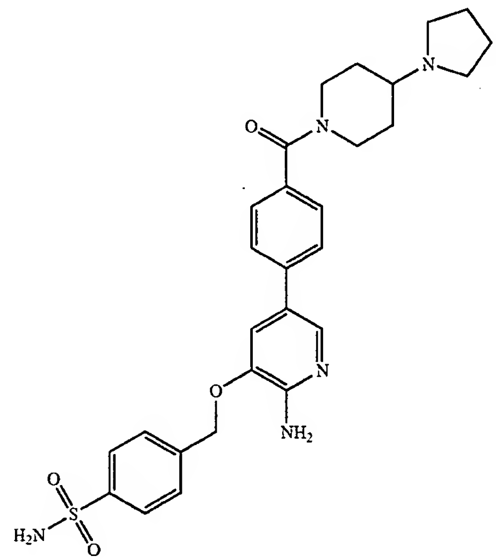
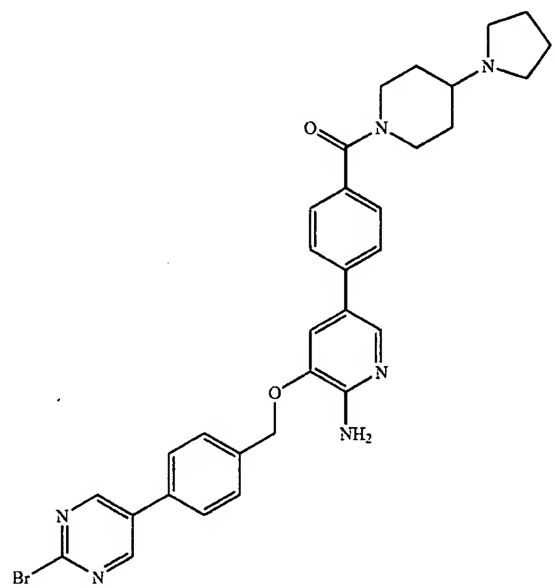
TABLE 7-continued





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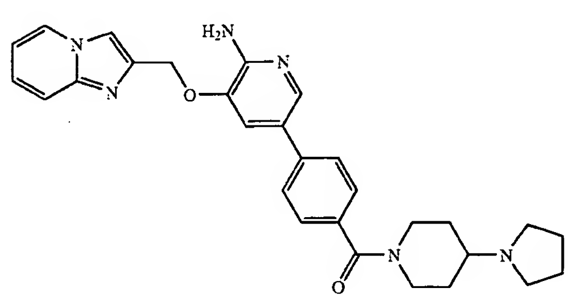

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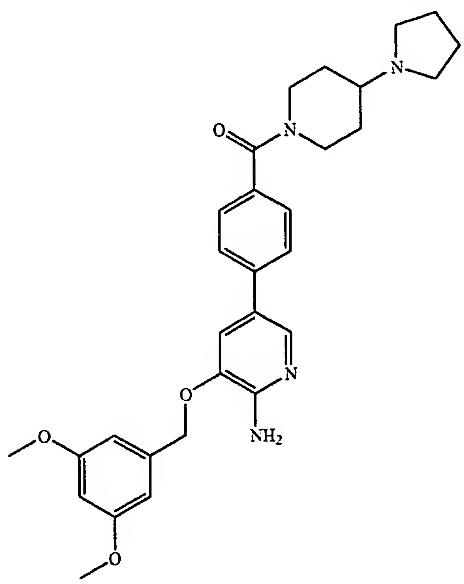
TABLE 7-continued



% Inhibition = 17

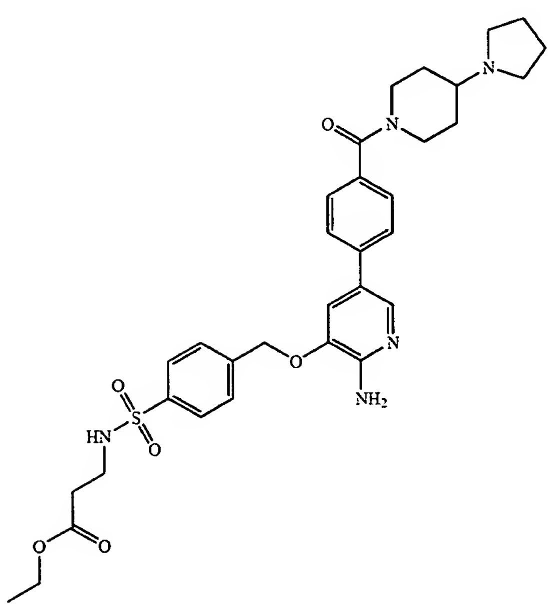


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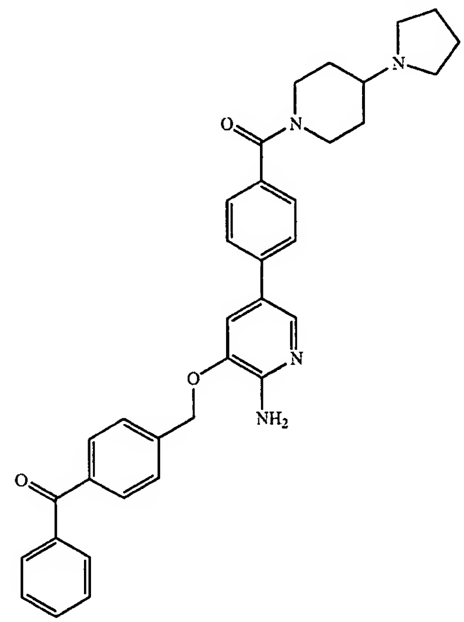
TABLE 7-continued



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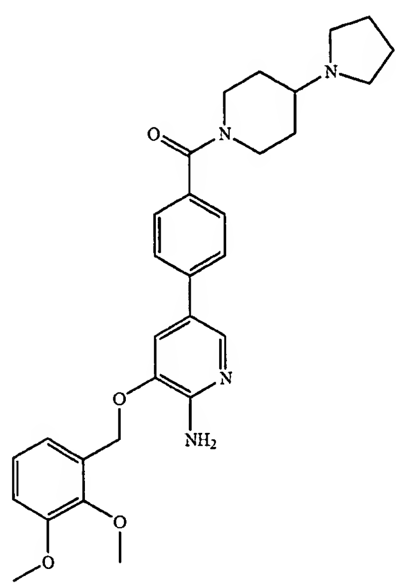

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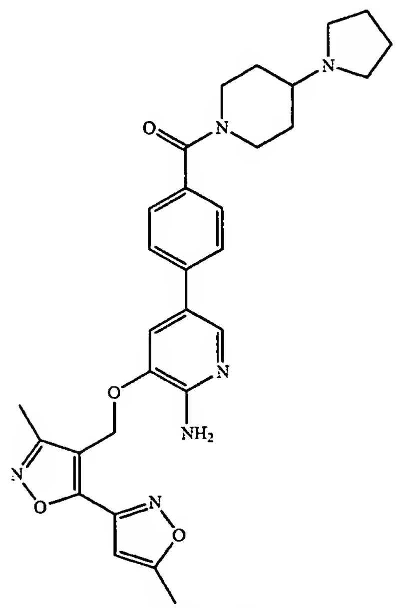
TABLE 7-continued



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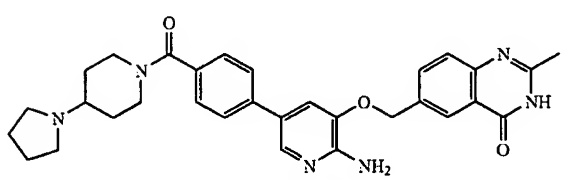

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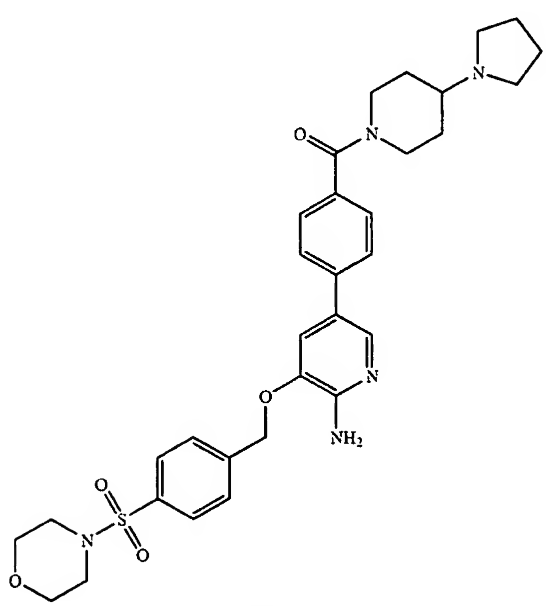
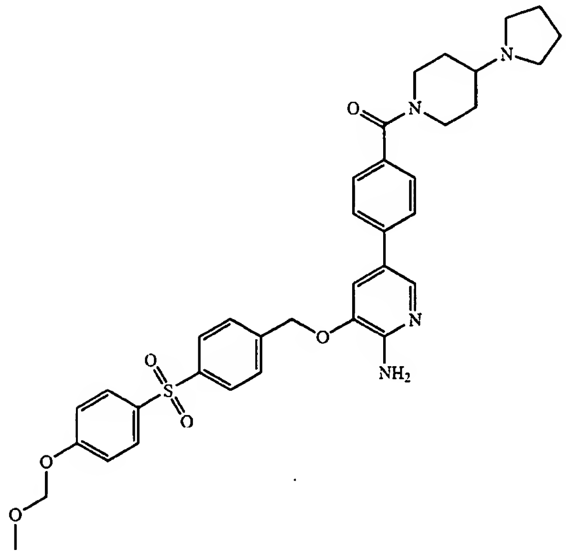
Section H: Examples L-465 to L480



% Inhibition = 14

TABLE 7-continued



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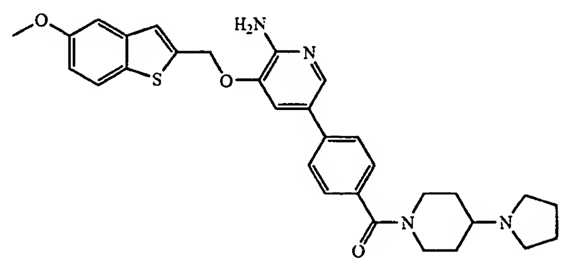

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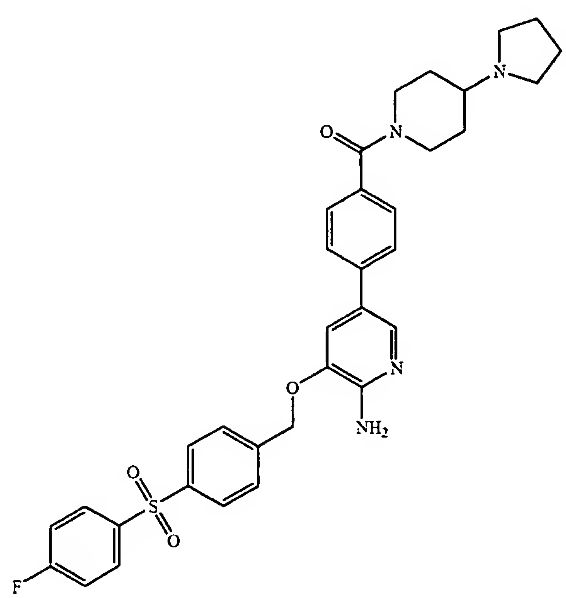

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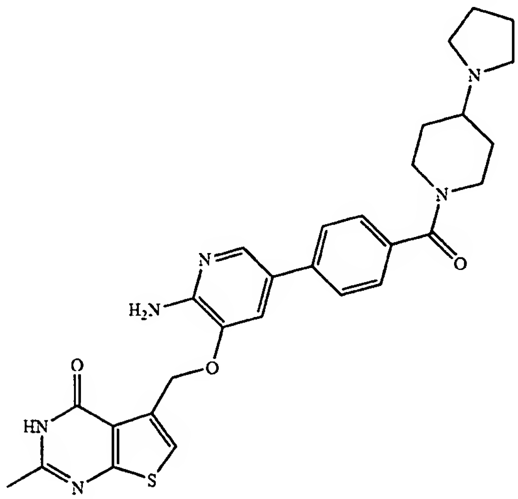

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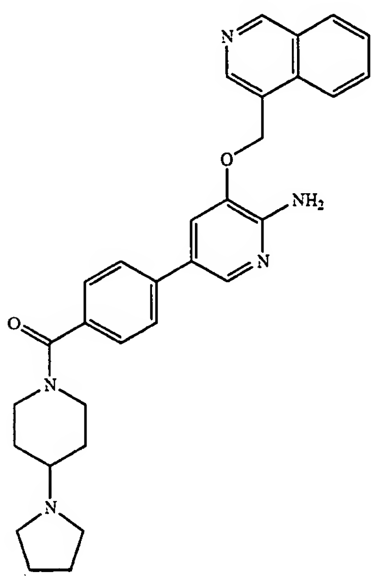

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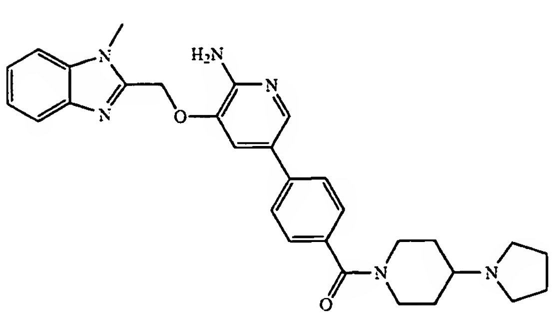

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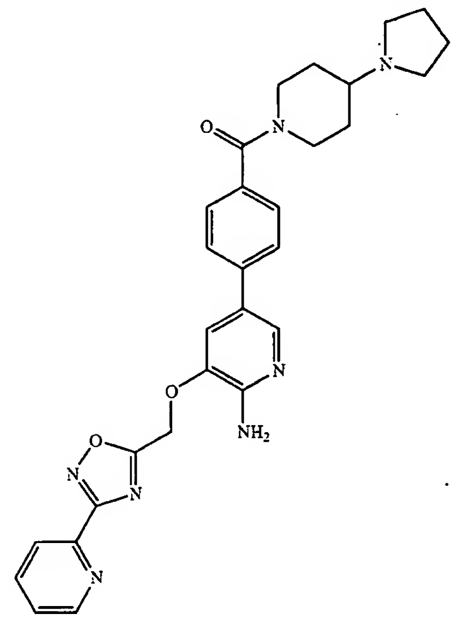
TABLE 7-continued



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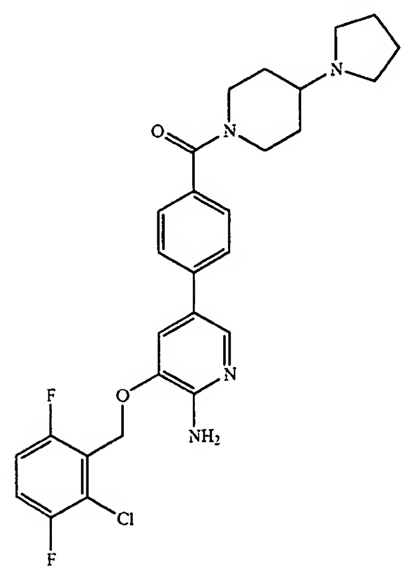

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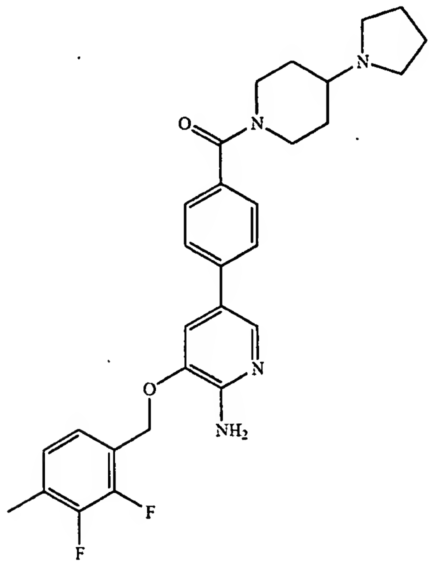
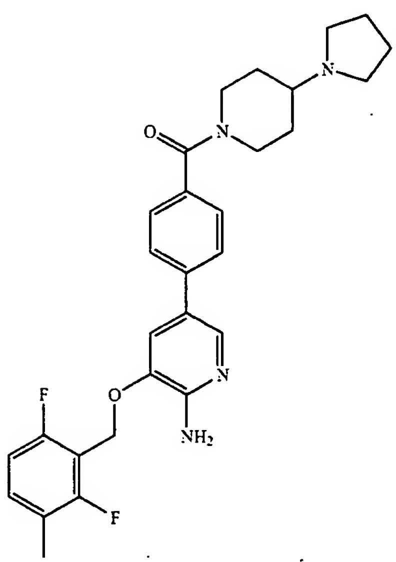


% Inhibition = 39



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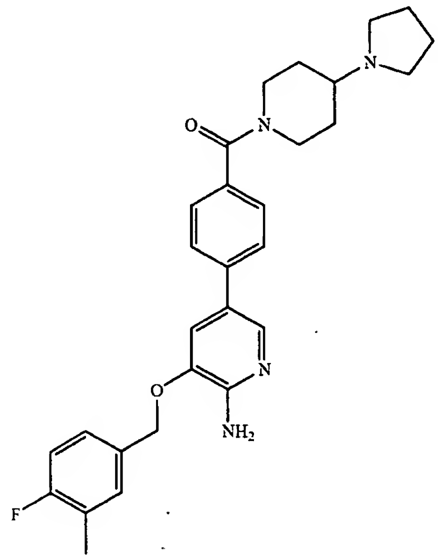

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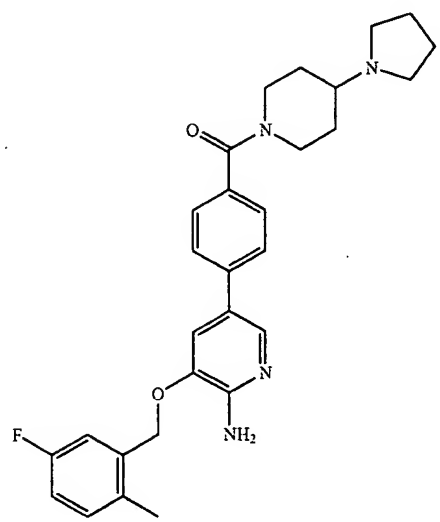

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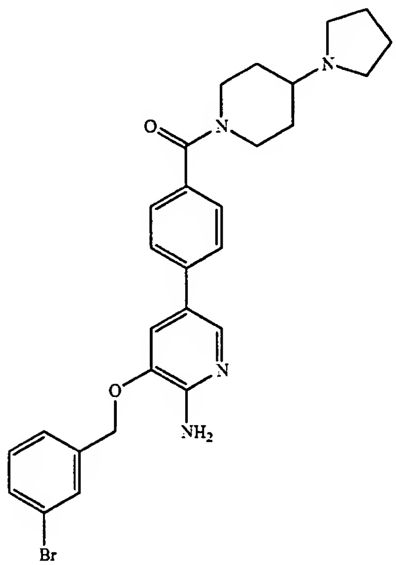
TABLE 7-continued



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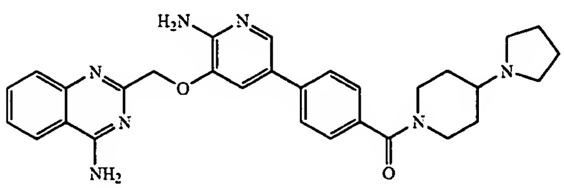

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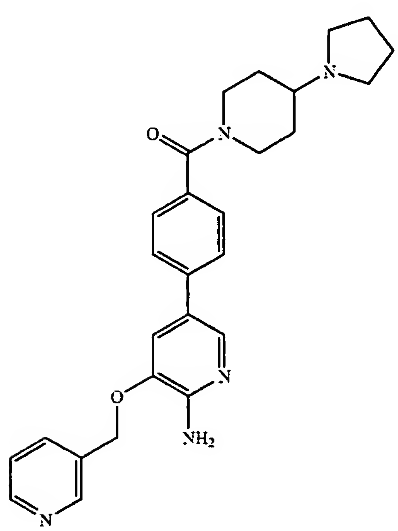
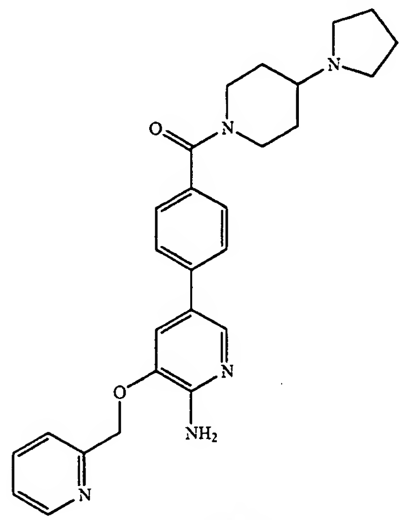


% Inhibition = 17

TABLE 7-continued

Section I: Examples L-481 to L496



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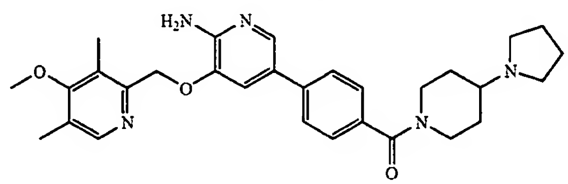

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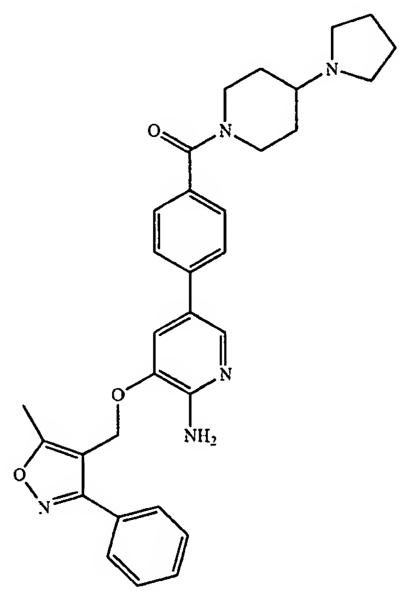

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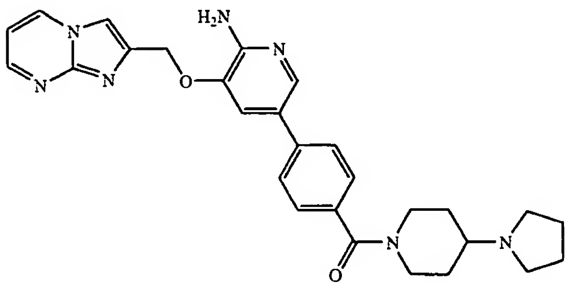
TABLE 7-continued



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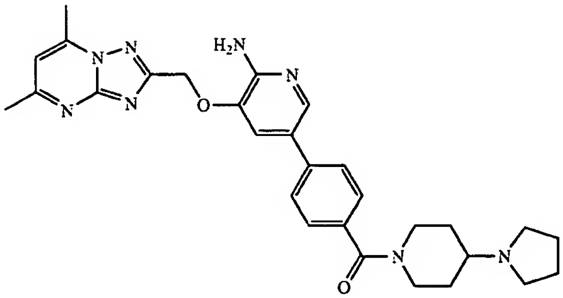

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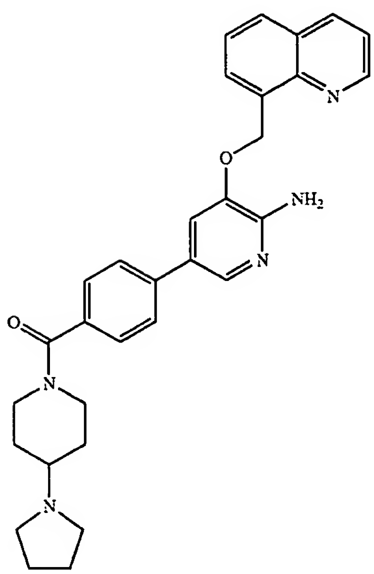

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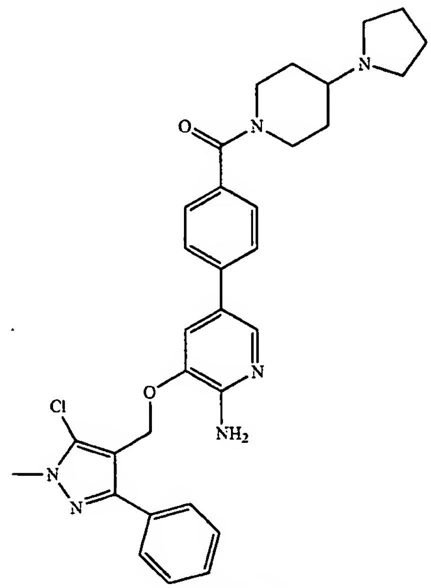
TABLE 7-continued



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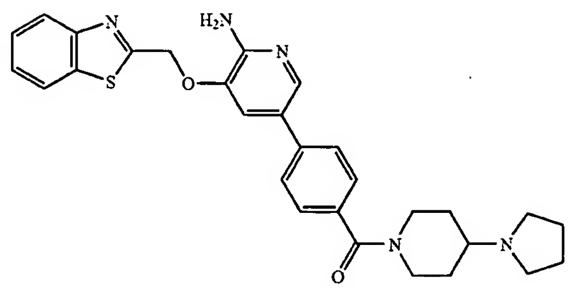

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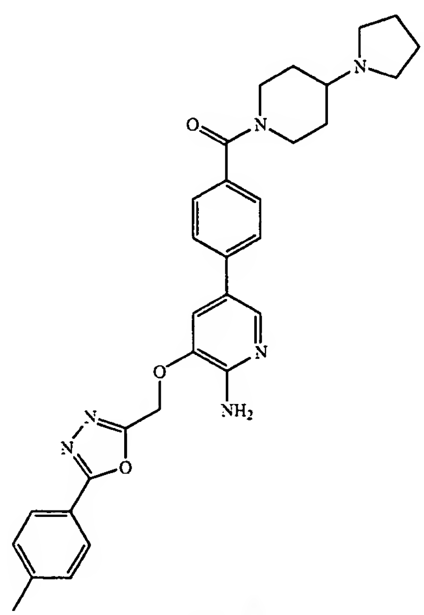

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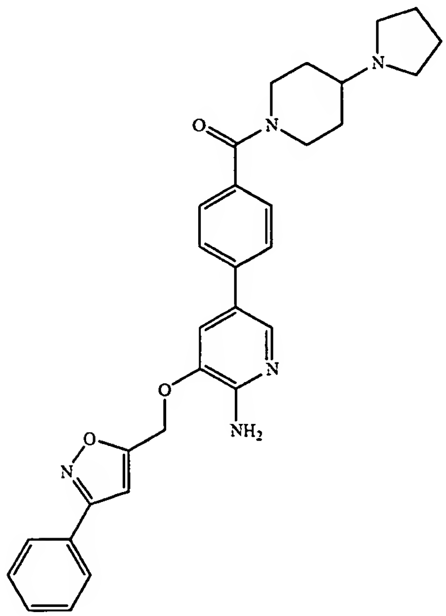
TABLE 7-continued



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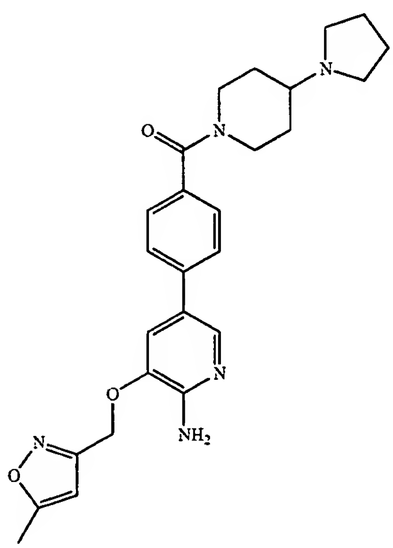

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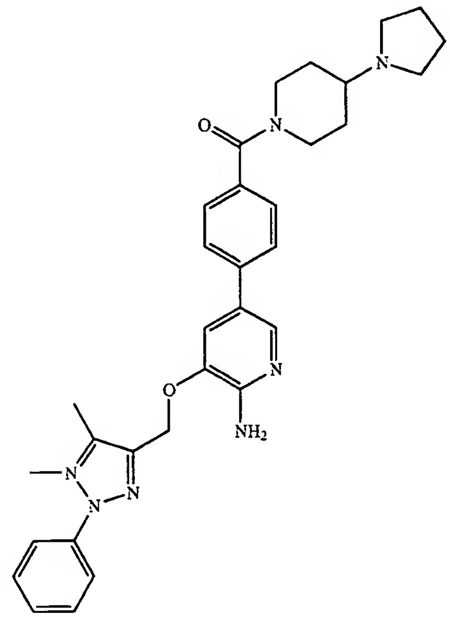
TABLE 7-continued



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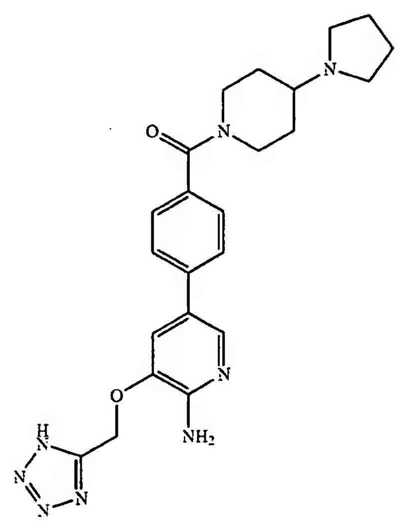

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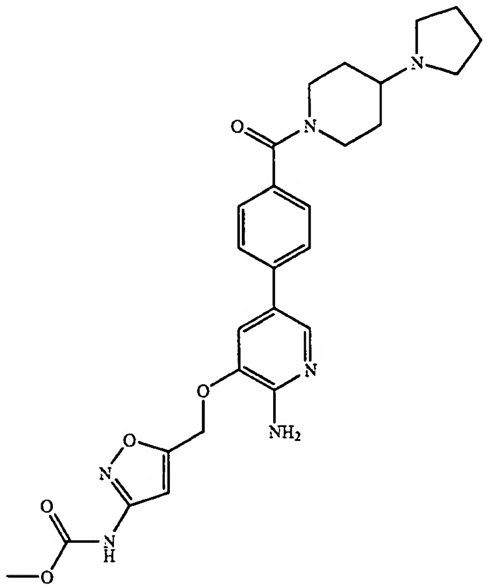
TABLE 7-continued



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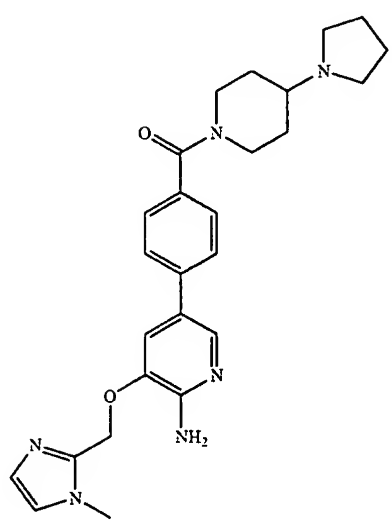

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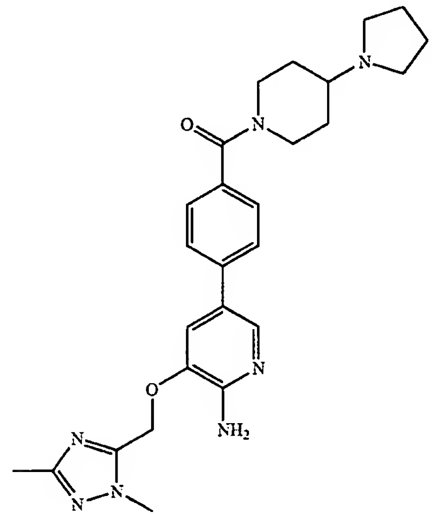
TABLE 7-continued



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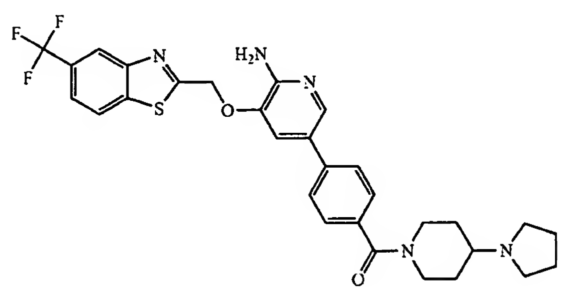
Section J: Examples L-497 to L-512



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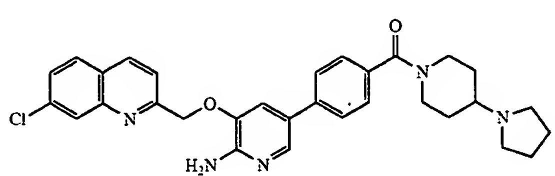

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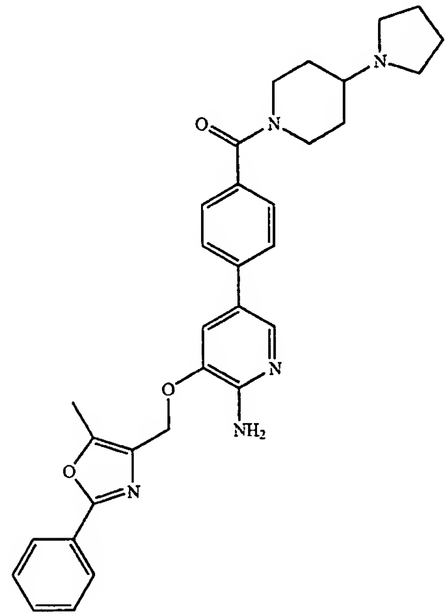
TABLE 7-continued



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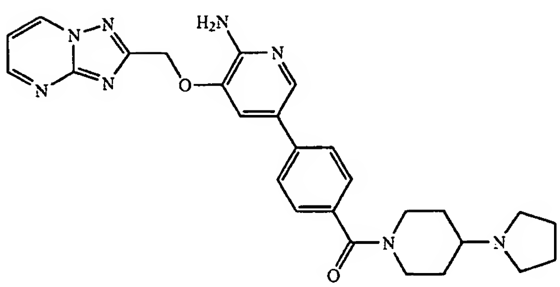

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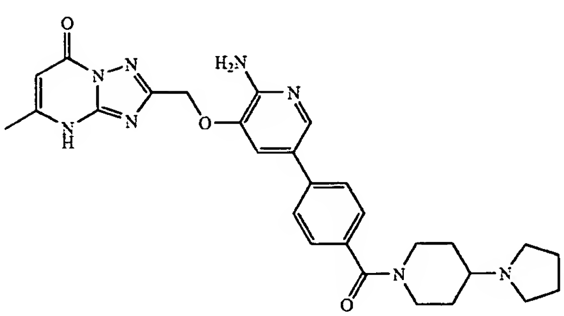

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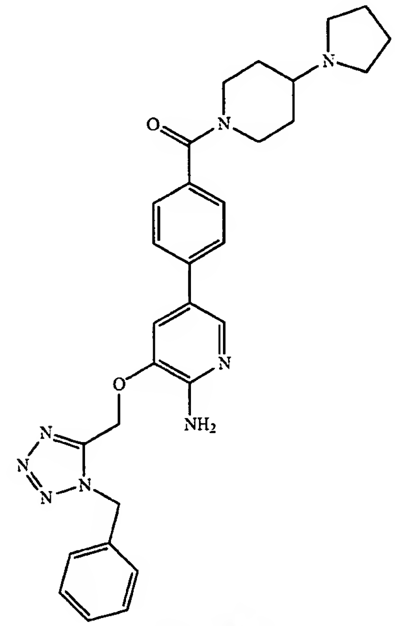
TABLE 7-continued



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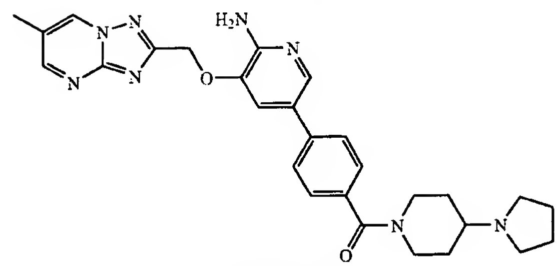

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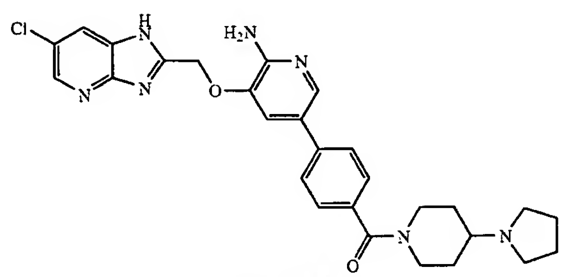

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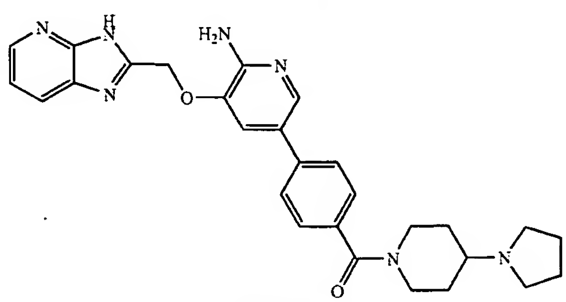

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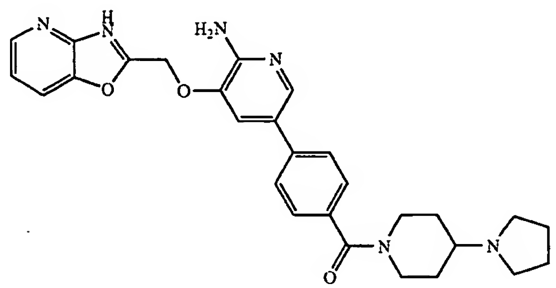
TABLE 7-continued



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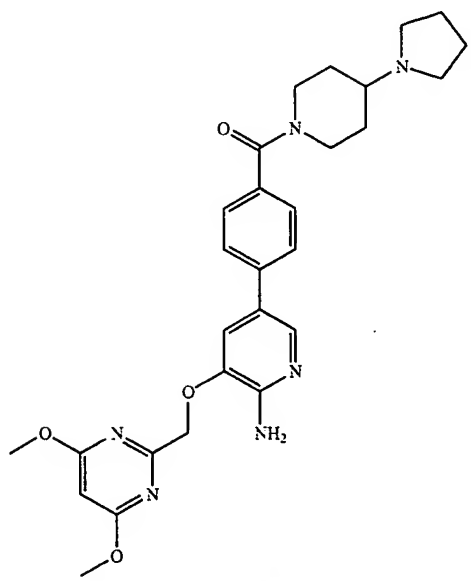

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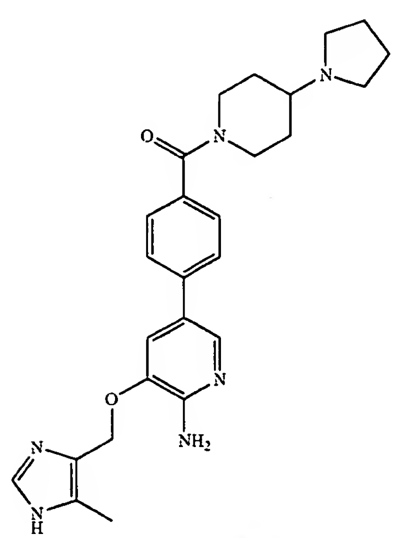

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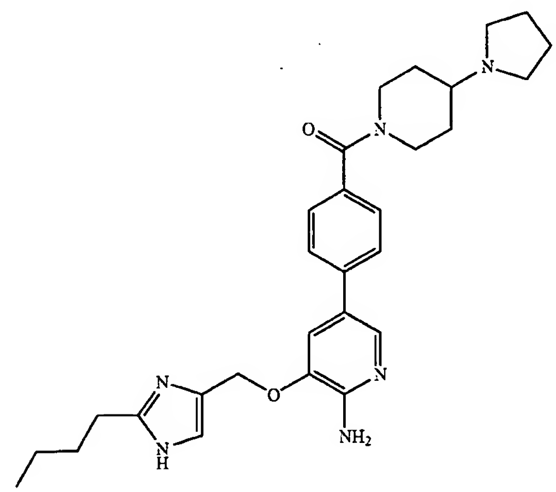
TABLE 7-continued



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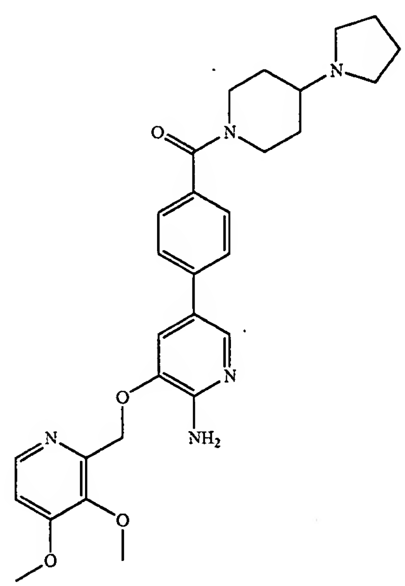

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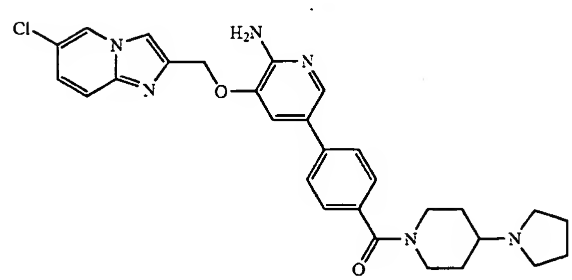

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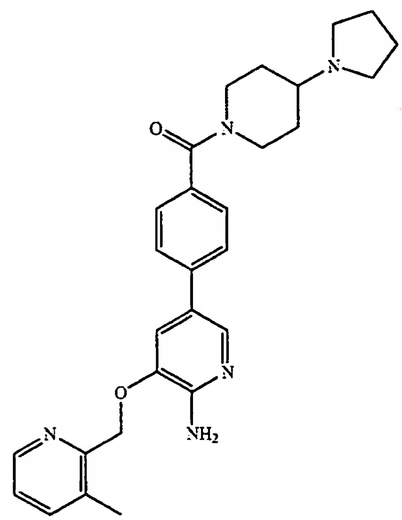
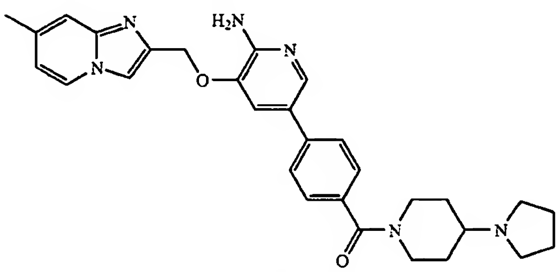
TABLE 7-continued



% Inhibition = 16

Section K: Examples L-513 to L-528



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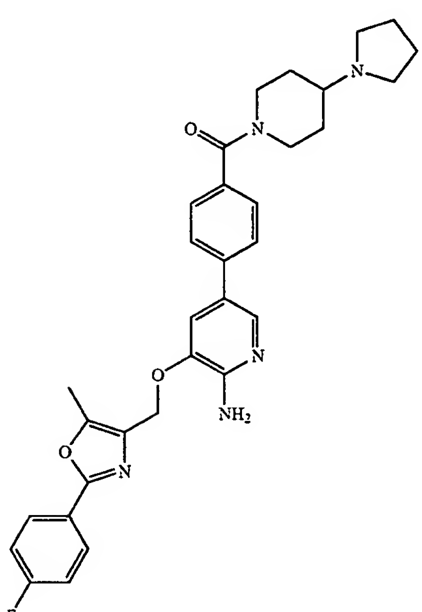

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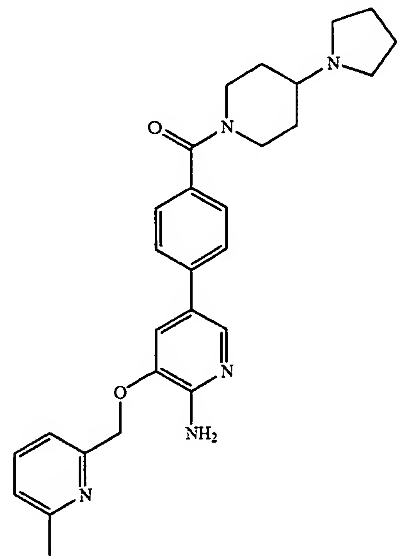
TABLE 7-continued



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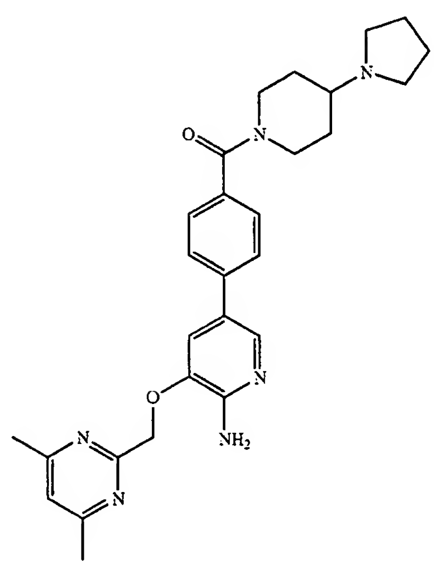

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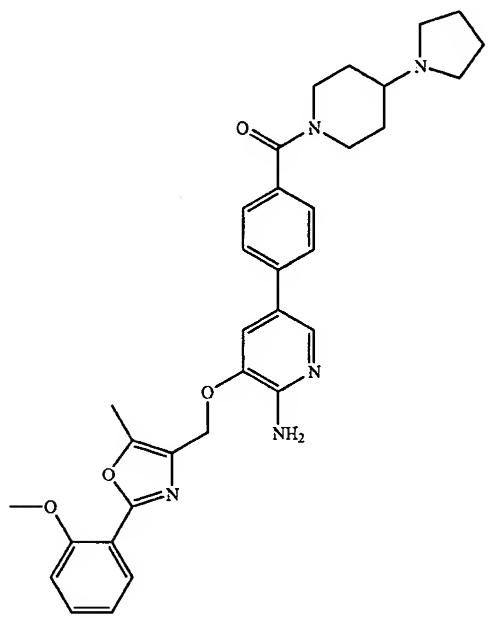
TABLE 7-continued



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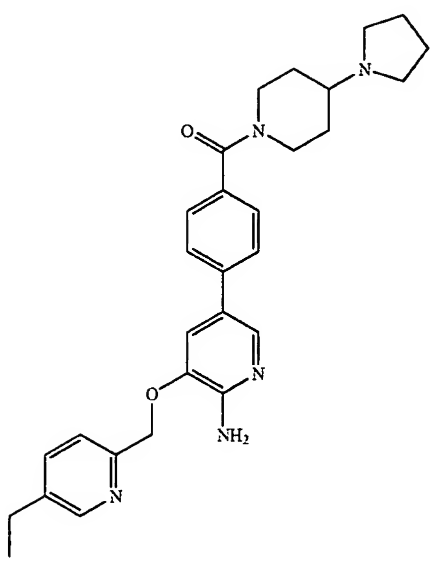

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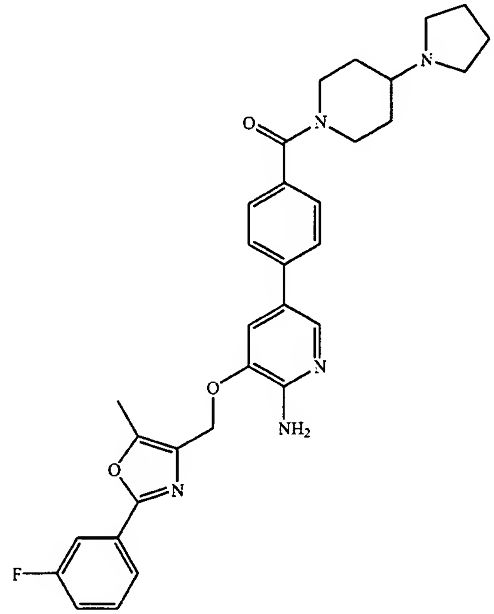

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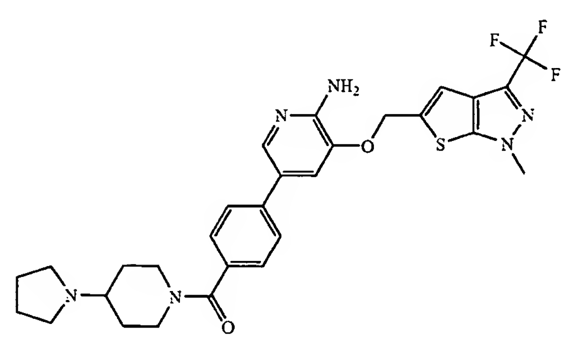

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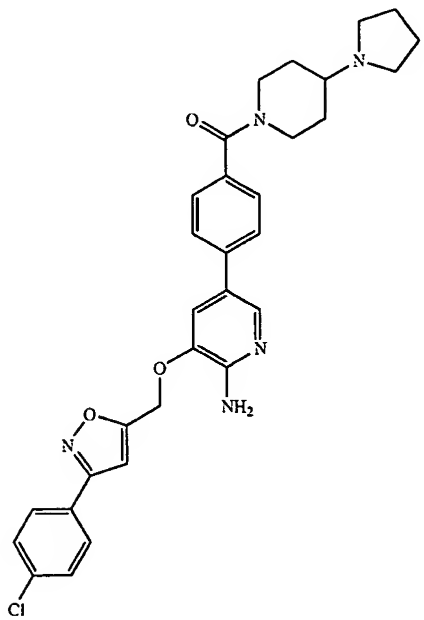

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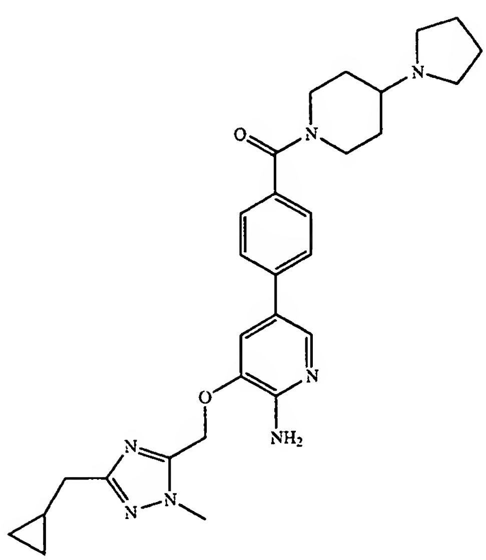

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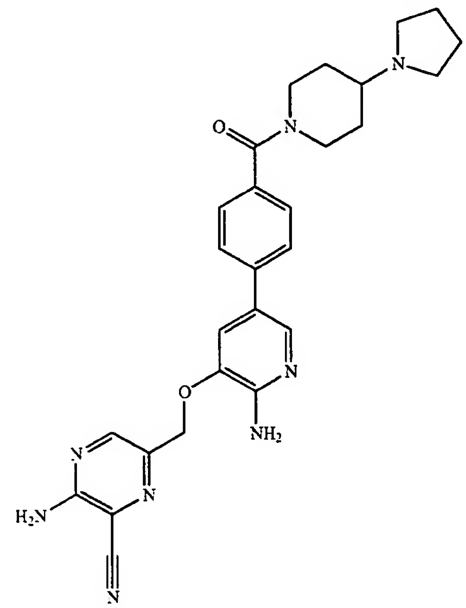
TABLE 7-continued



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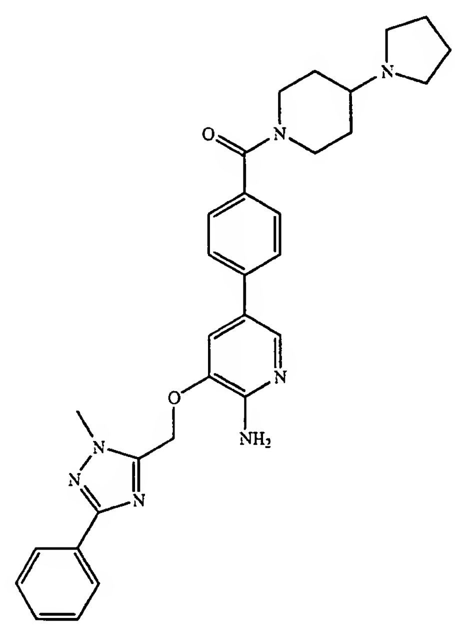

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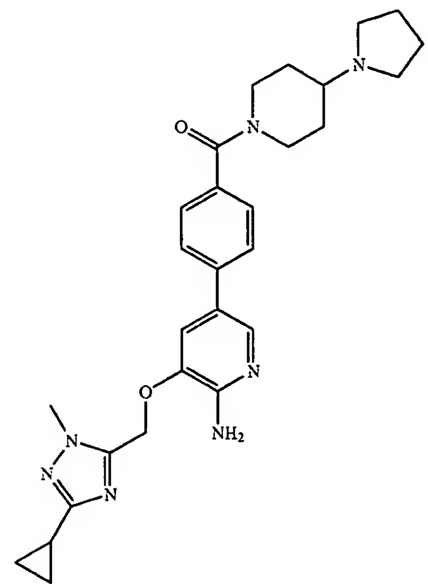

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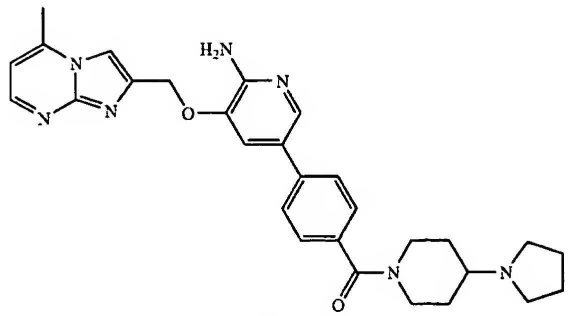

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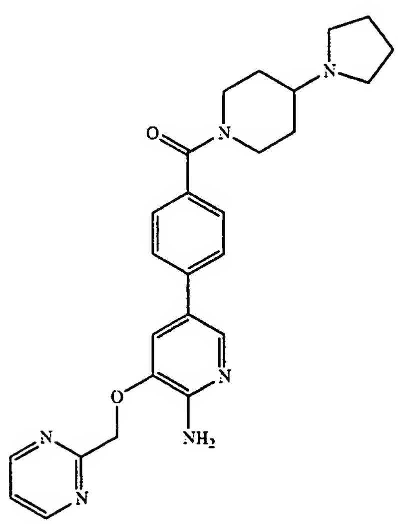

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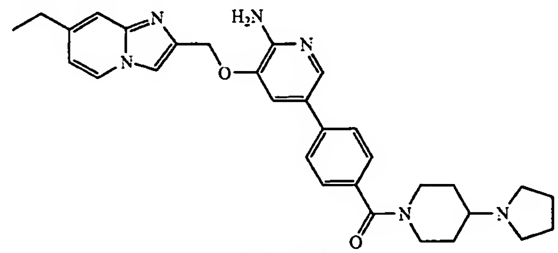
TABLE 7-continued



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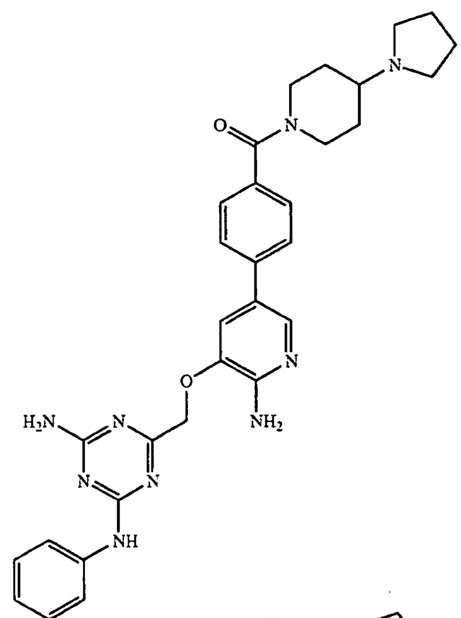
Section L: Examples L-529 to L-548



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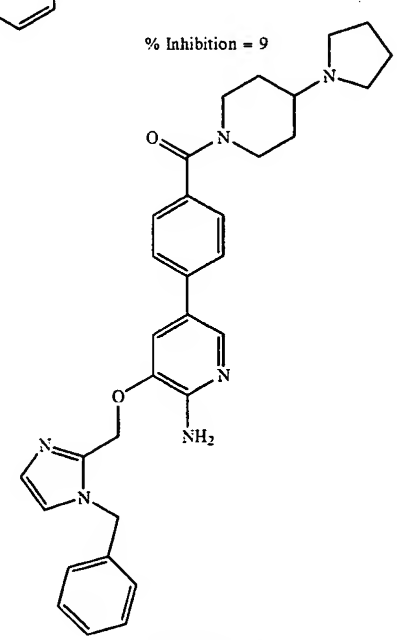

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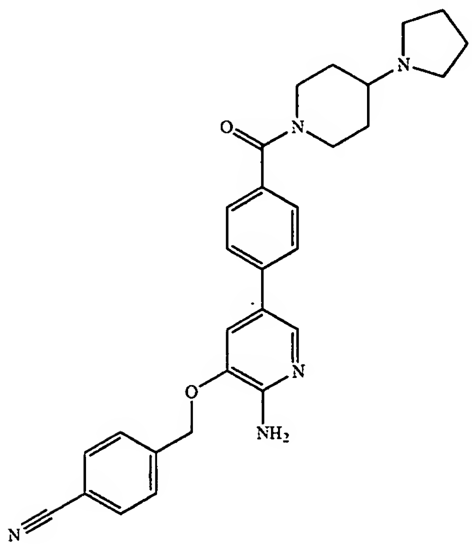

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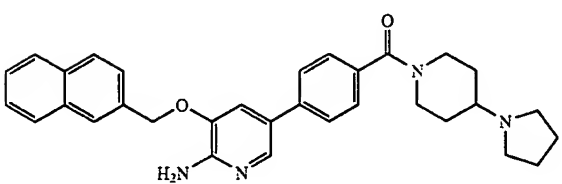

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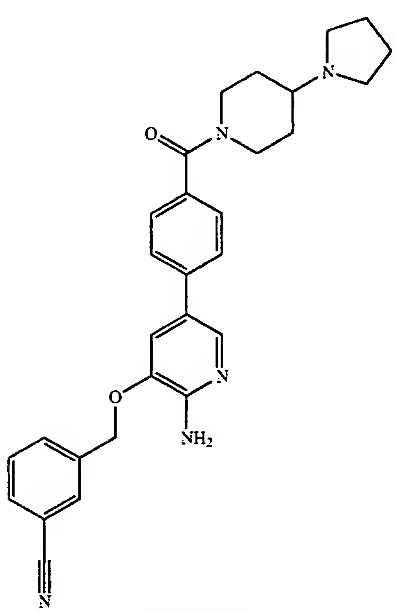

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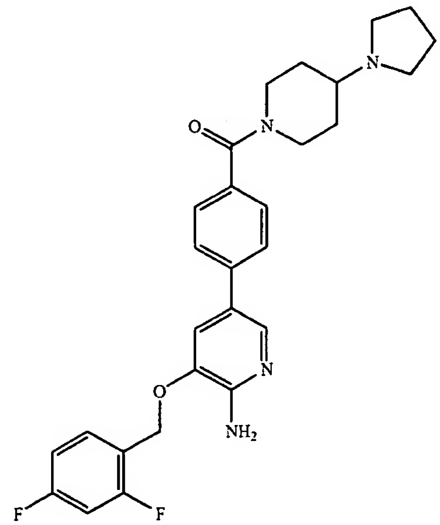
TABLE 7-continued



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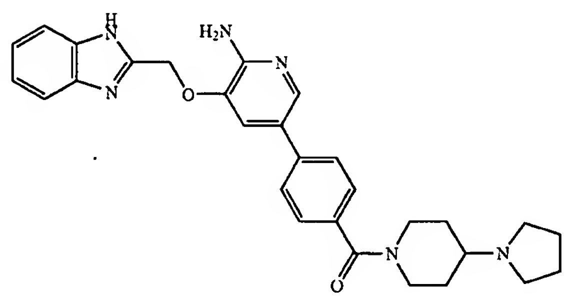

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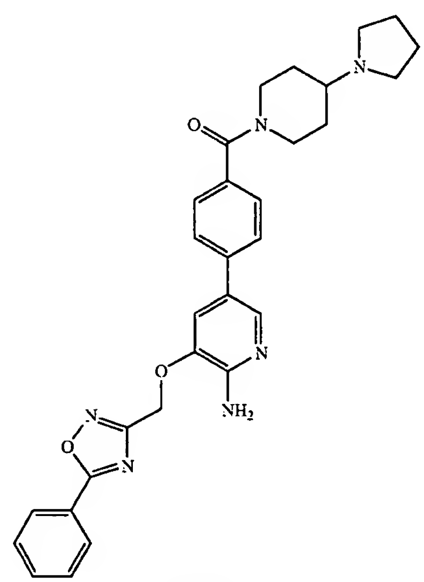

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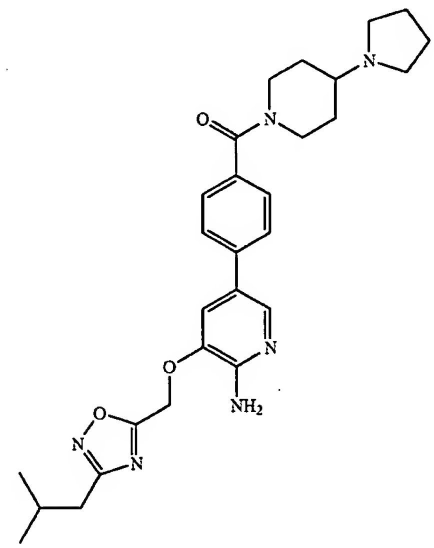
TABLE 7-continued



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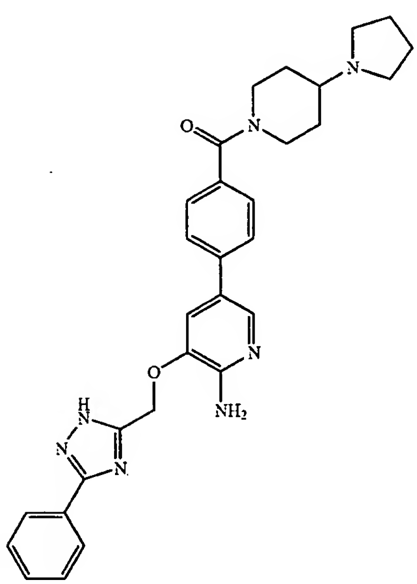

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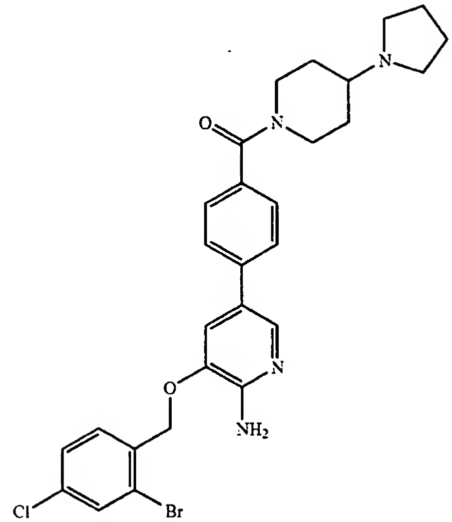

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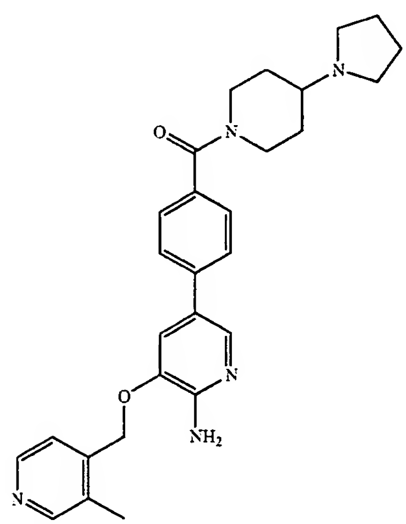

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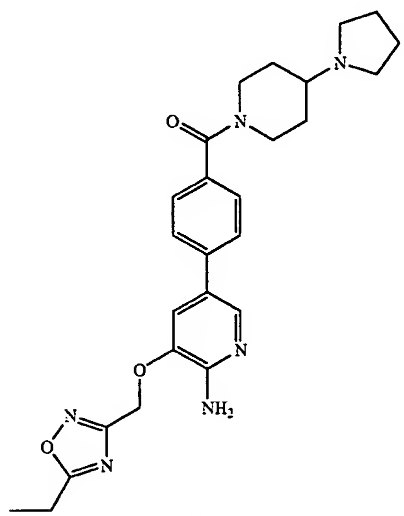
TABLE 7-continued



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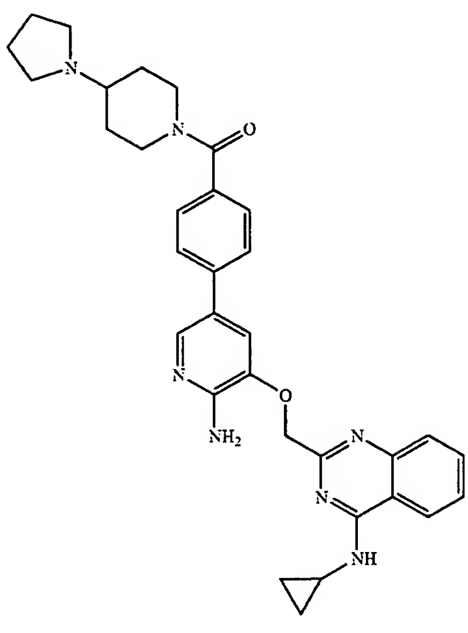

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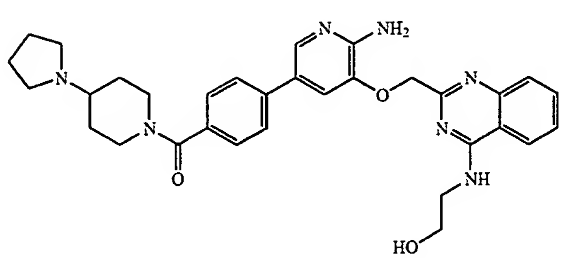
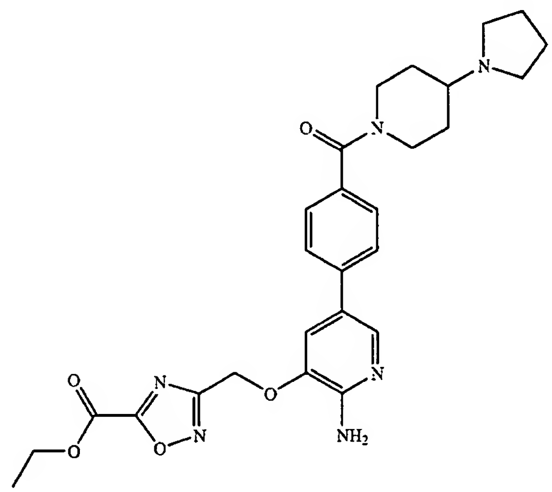


% Inhibition = 7

TABLE 7-continued



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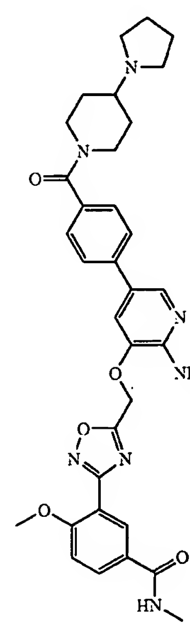
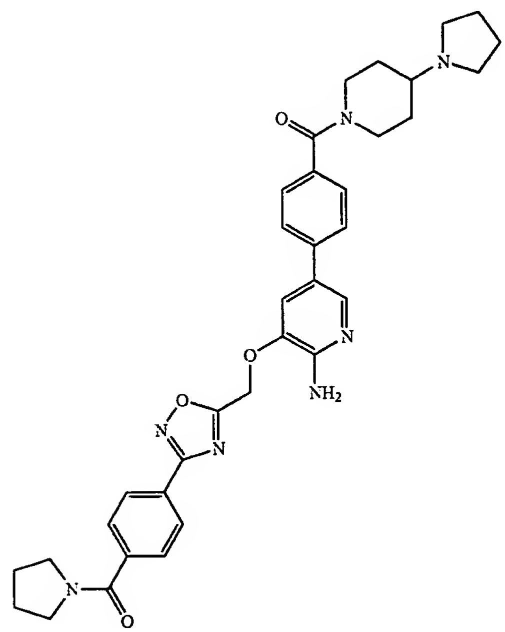


% Inhibition = 11

TABLE 7-continued



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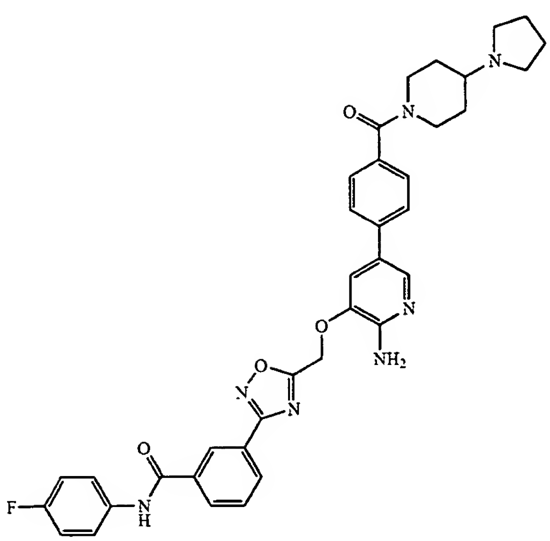

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TABLE 7-continued

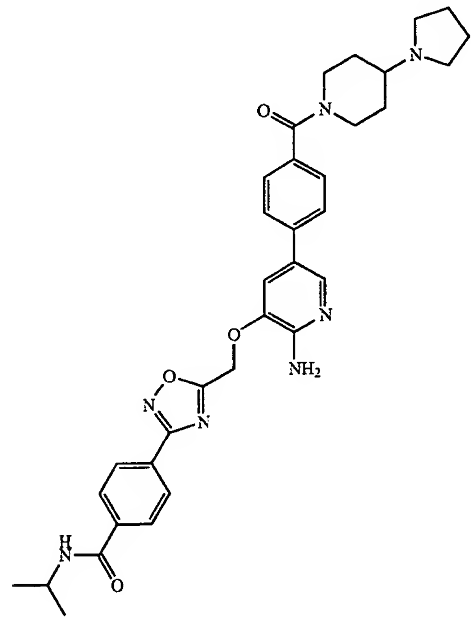

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TABLE 8

Section A: Examples L-549 to L-561

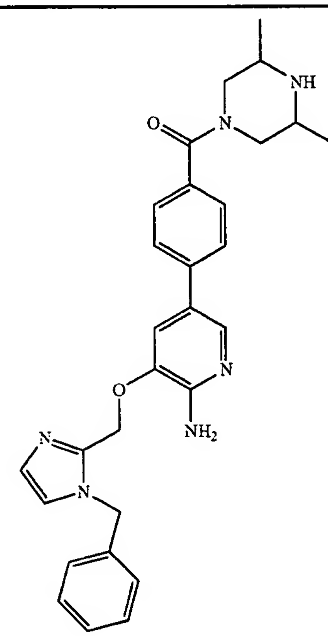

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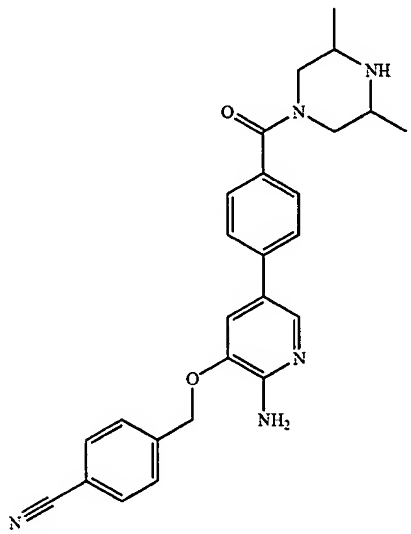
TABLE 8-continued



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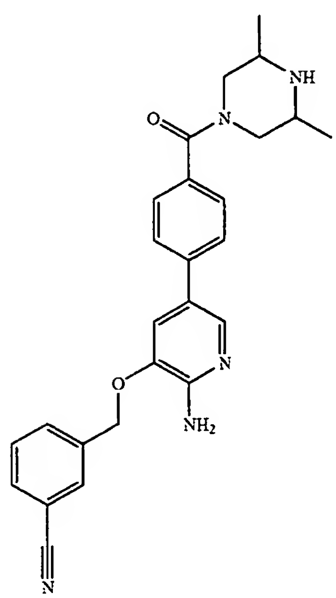

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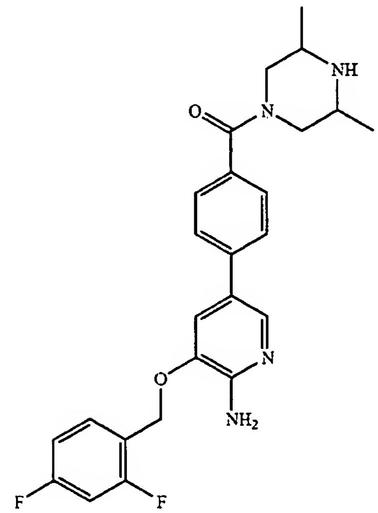
TABLE 8-continued



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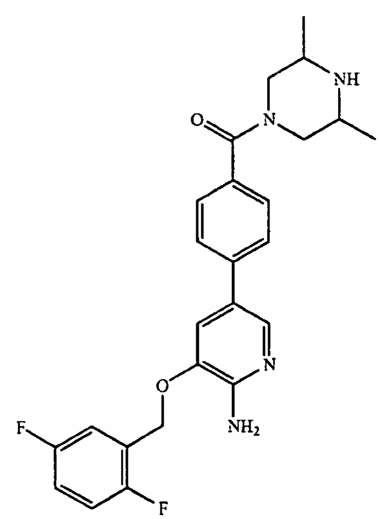

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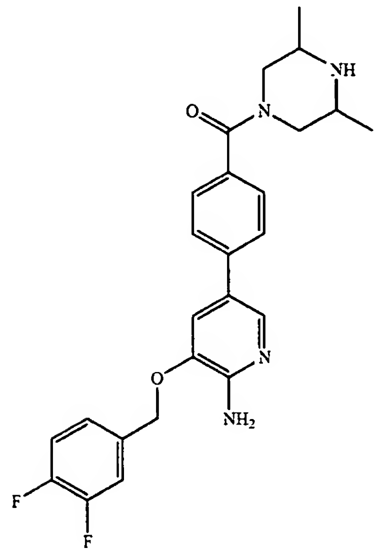
TABLE 8-continued



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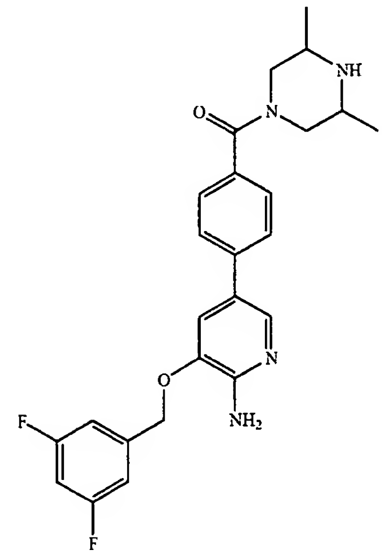

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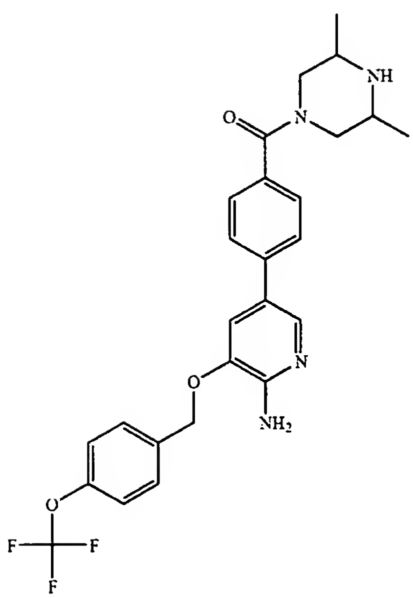

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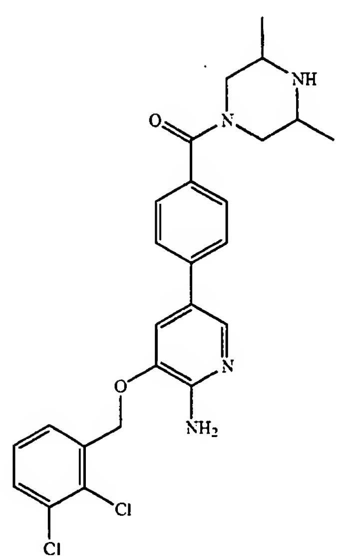

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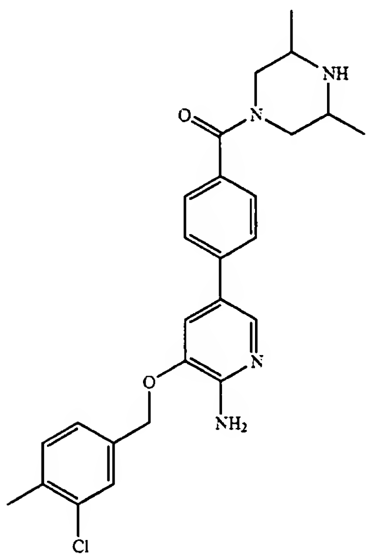
TABLE 8-continued



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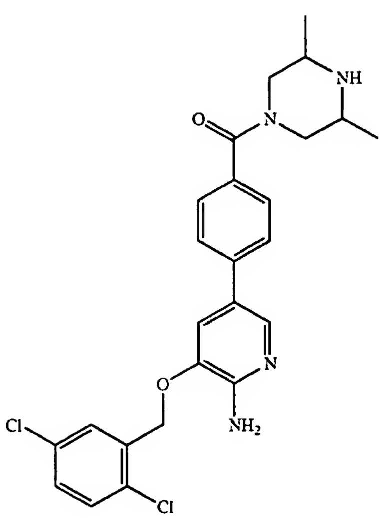

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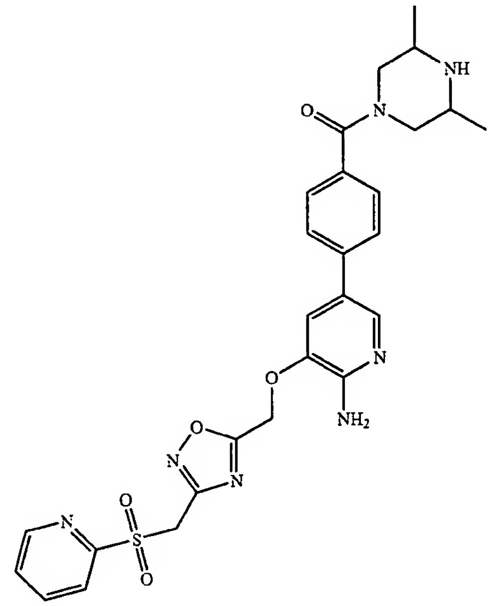
TABLE 8-continued



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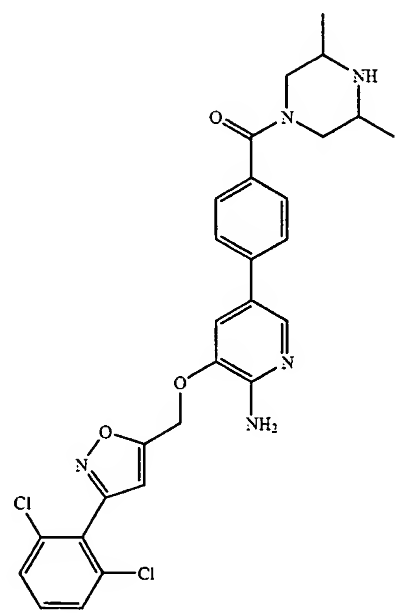

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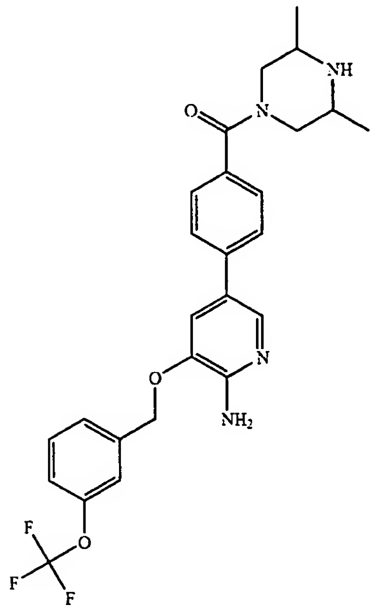
TABLE 8-continued



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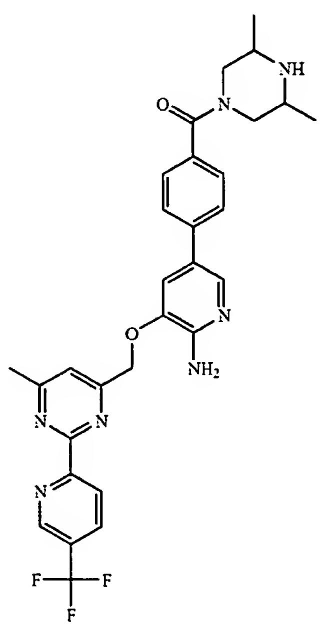

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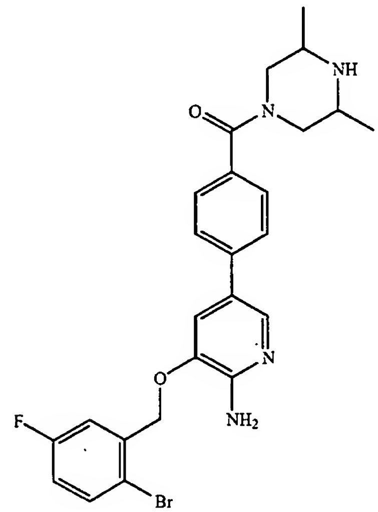
TABLE 8-continued



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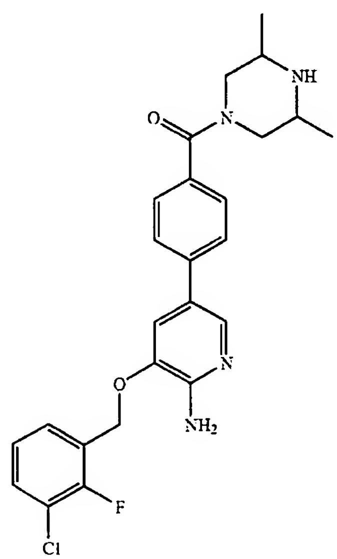
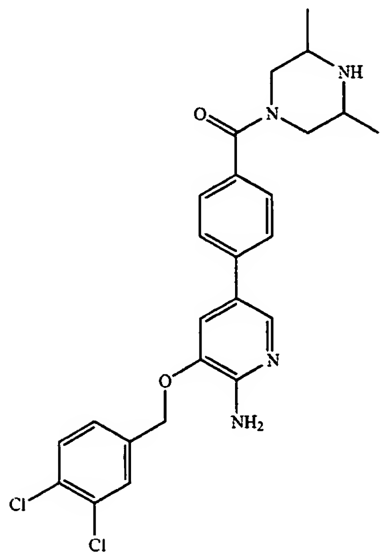
Section B: Examples L-565 to L-580



% Inhibition = 28

TABLE 8-continued



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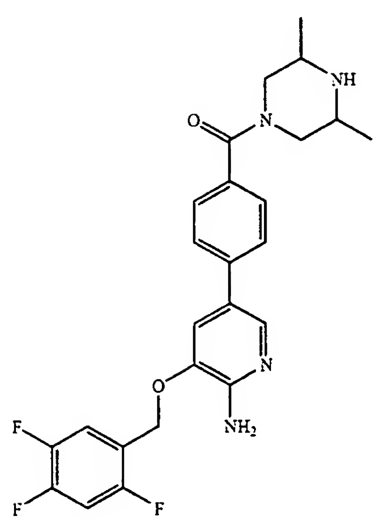

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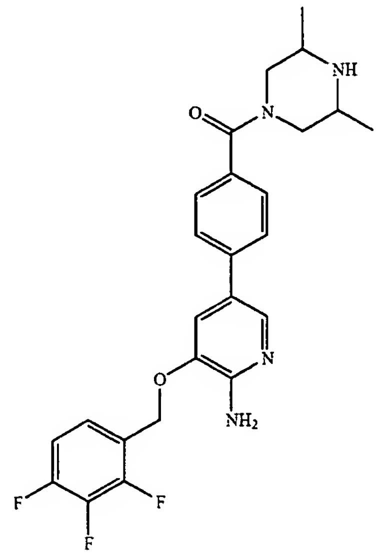
TABLE 8-continued



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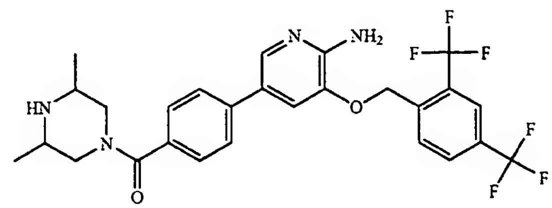

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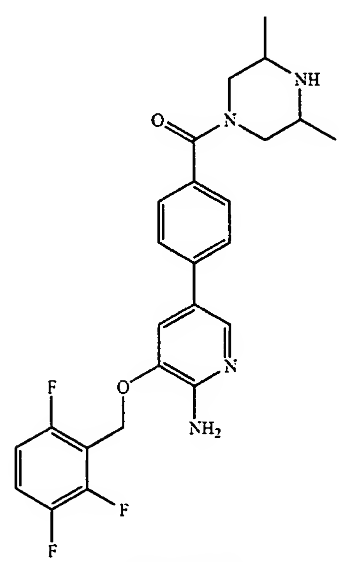

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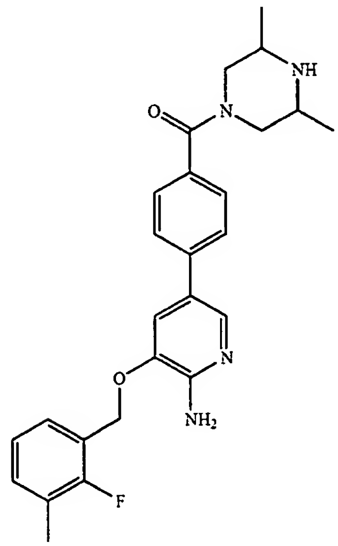
TABLE 8-continued



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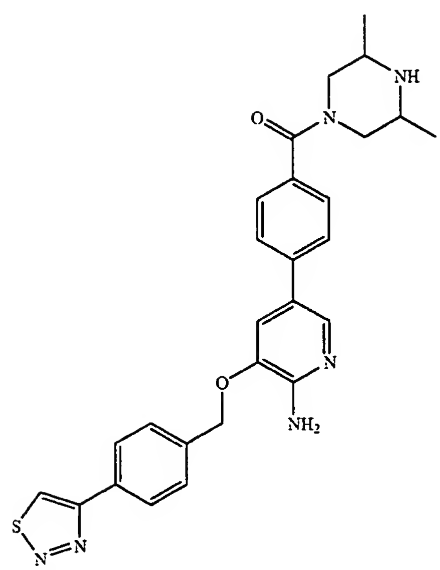

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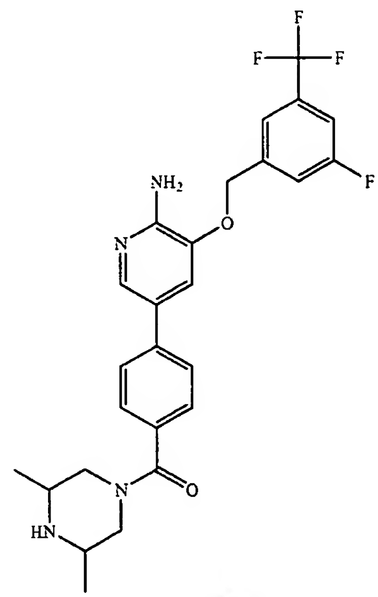
TABLE 8-continued



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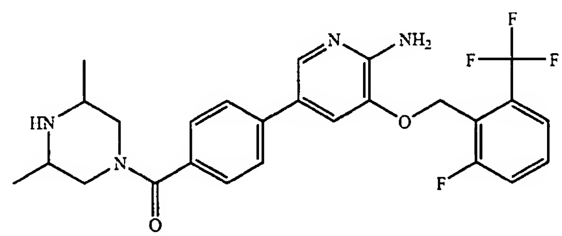
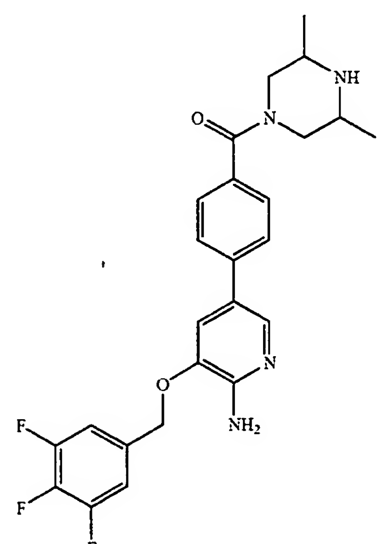
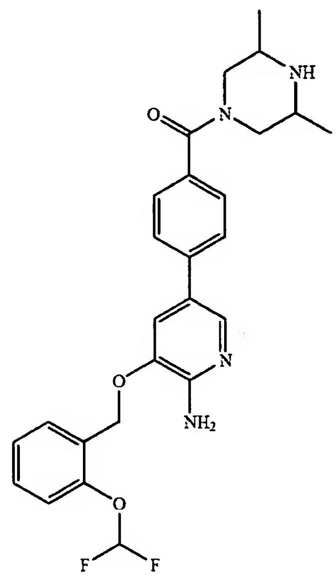


% Inhibition = 33

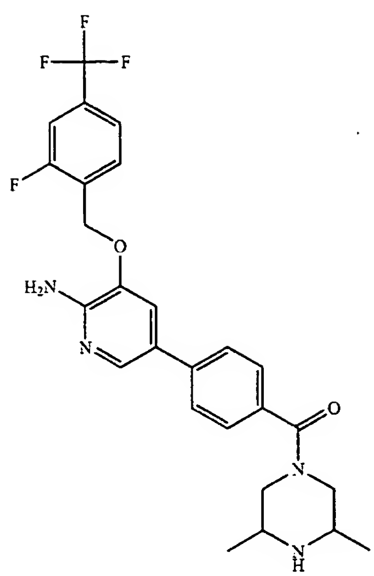


% Inhibition = 11

TABLE 8-continued

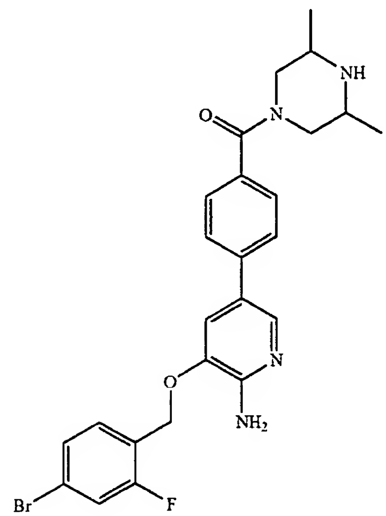


% Inhibition = 24

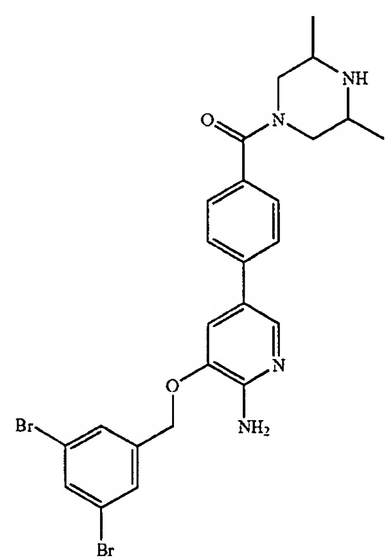


% Inhibition = 24

TABLE 8-continued

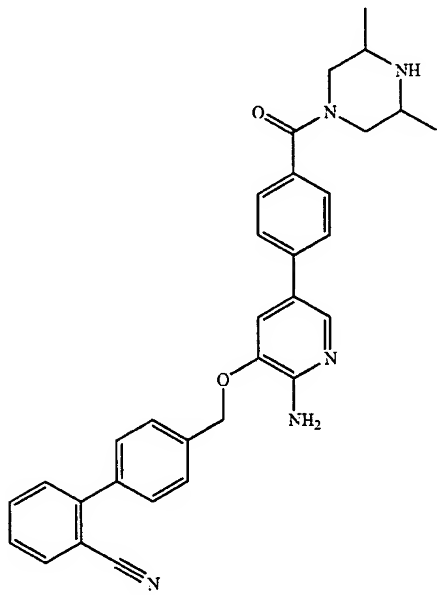


% Inhibition = 29

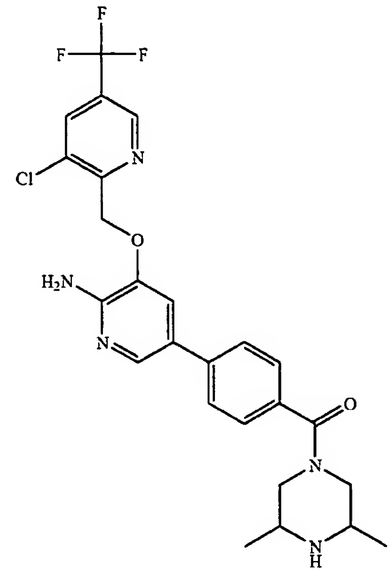


% Inhibition = 42

TABLE 8-continued

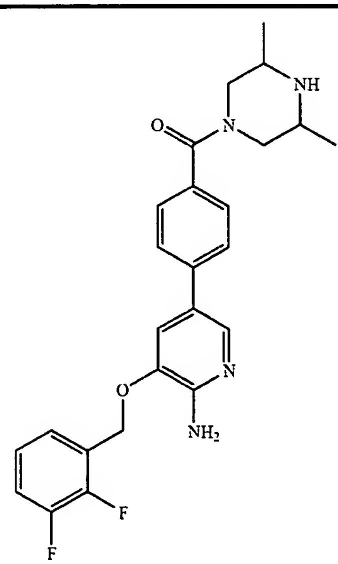


% Inhibition = 73

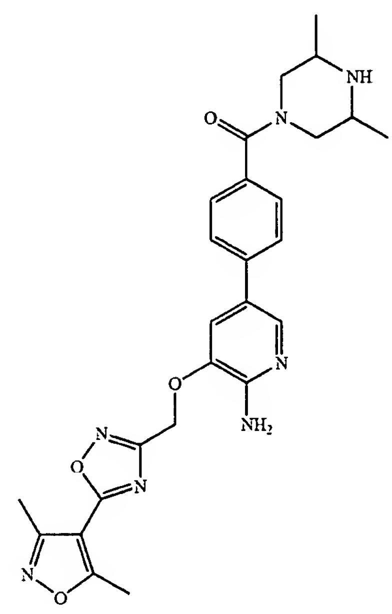


% Inhibition = 17

Section C: Examples L-581 to L-596

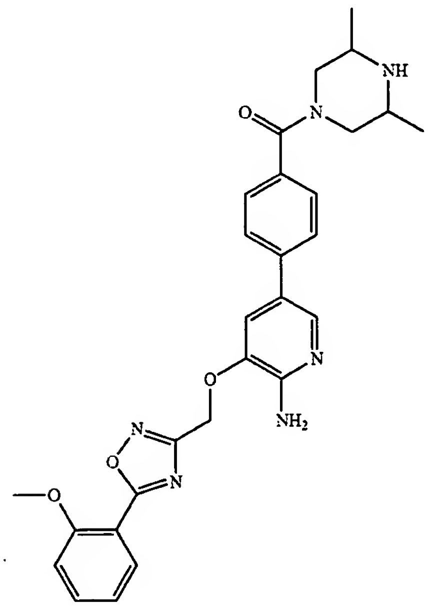


% Inhibition = 19

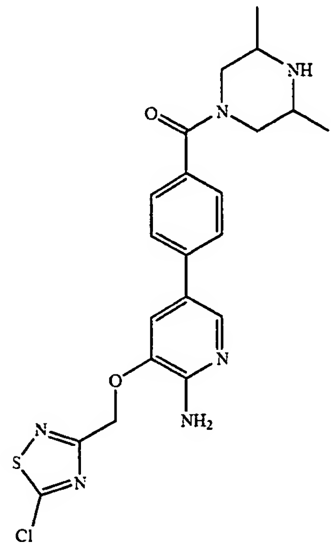


% Inhibition = 14

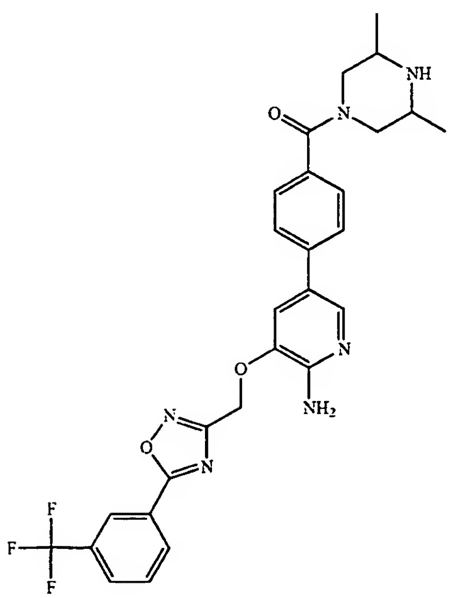
TABLE 8-continued



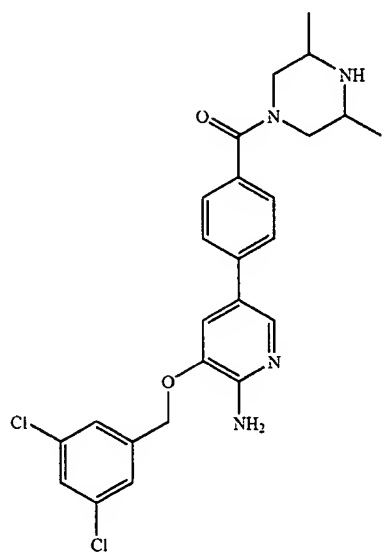
% Inhibition = 9



% Inhibition = 6

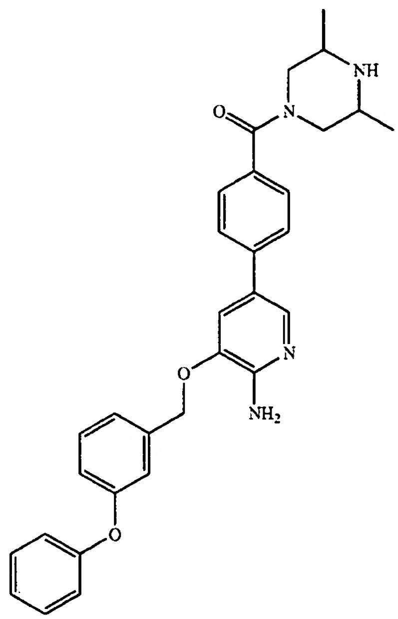


% Inhibition = 30

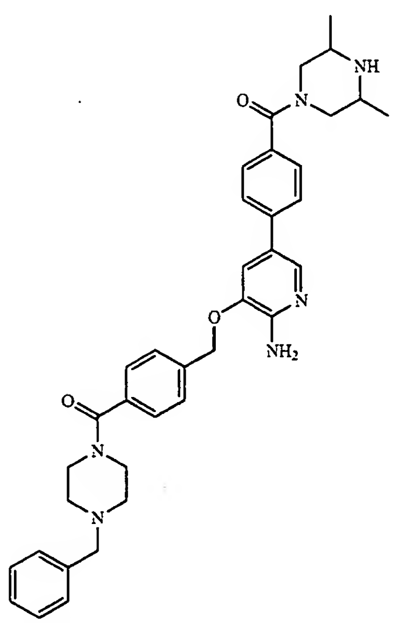


% Inhibition = 26

TABLE 8-continued

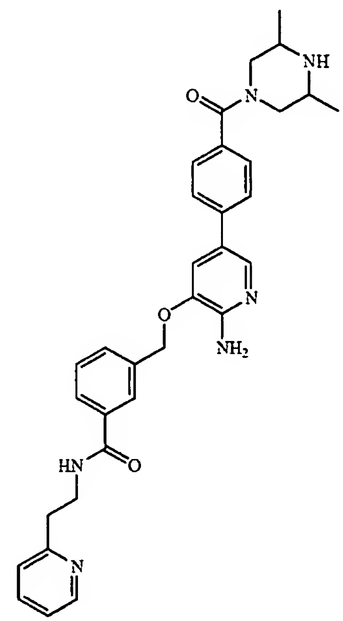


% Inhibition = 32

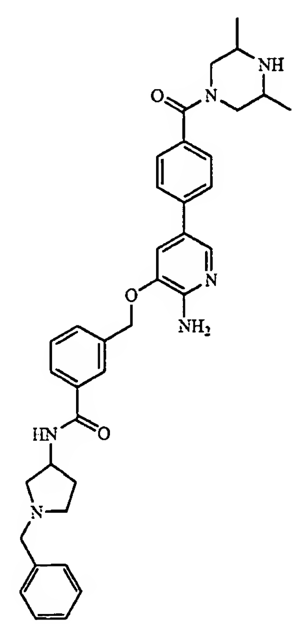


% Inhibition = 15

TABLE 8-continued

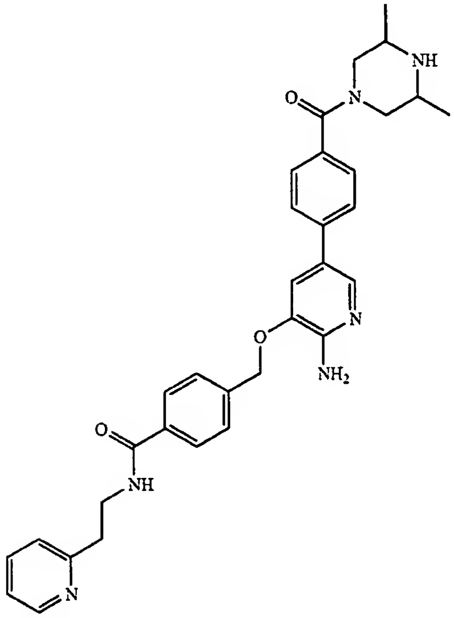


% Inhibition = 18

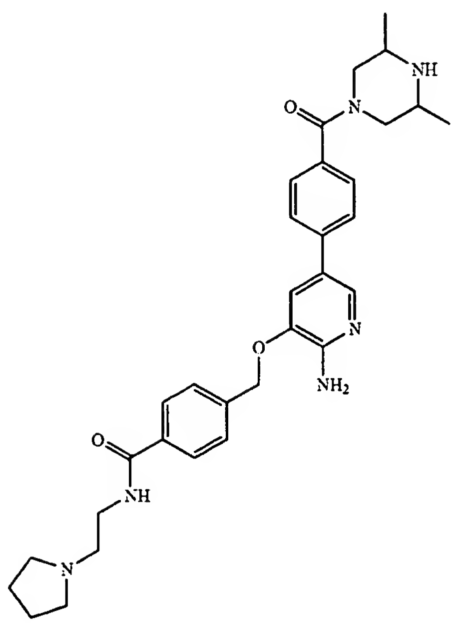


% Inhibition = 18

TABLE 8-continued

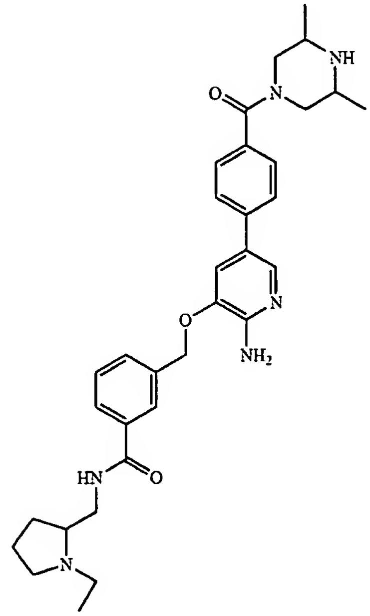


% Inhibition = 19



% Inhibition = 12

TABLE 8-continued



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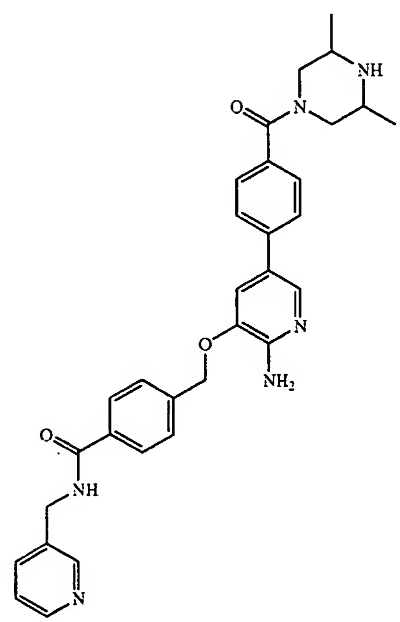
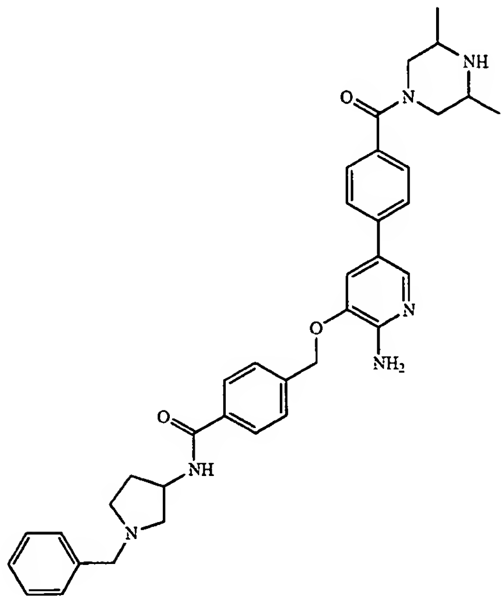


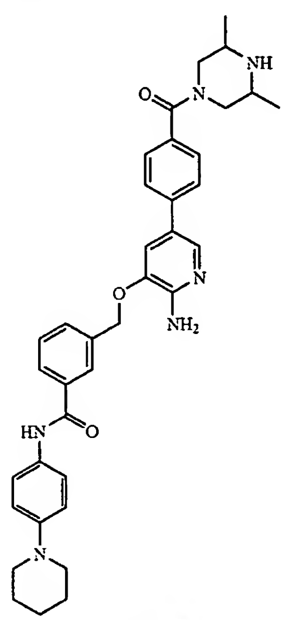
% Inhibition = 8

TABLE 8-continued

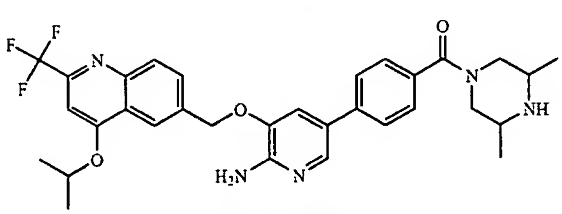


% Inhibition = 19

Section D: Examples L-597 to L-612

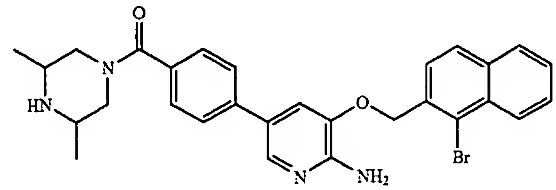


% Inhibition = 28

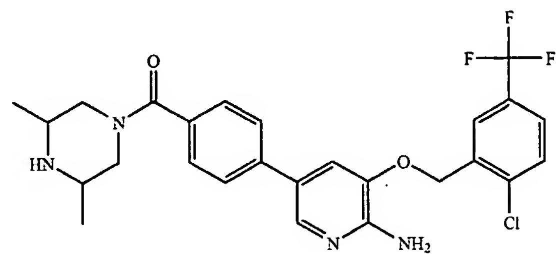


% Inhibition = 17

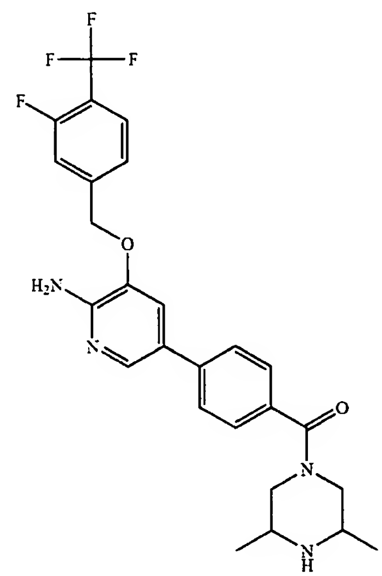
TABLE 8-continued



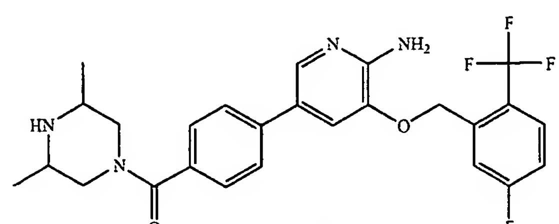
% Inhibition = 58



% Inhibition = 25

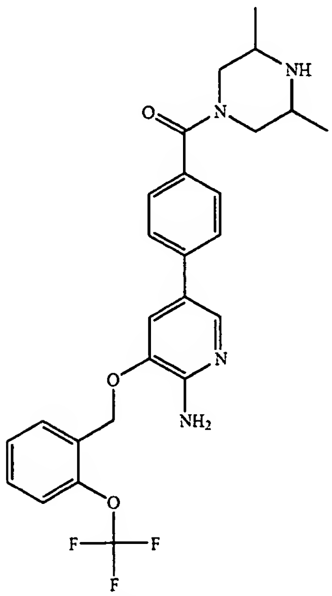


% Inhibition = 17



% Inhibition = 17

TABLE 8-continued



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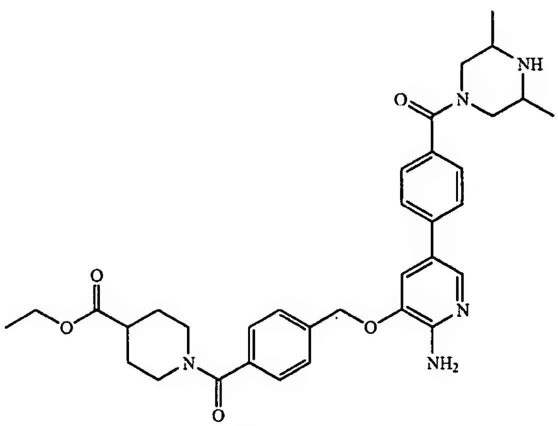
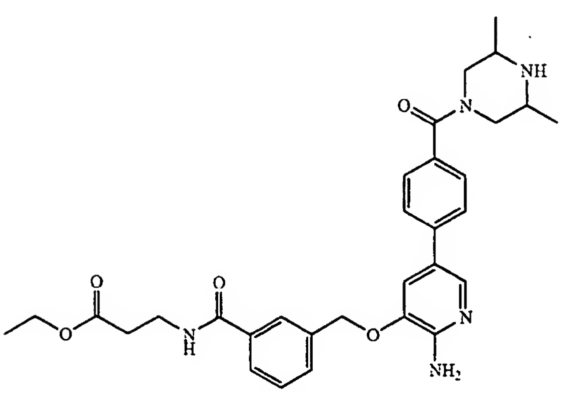
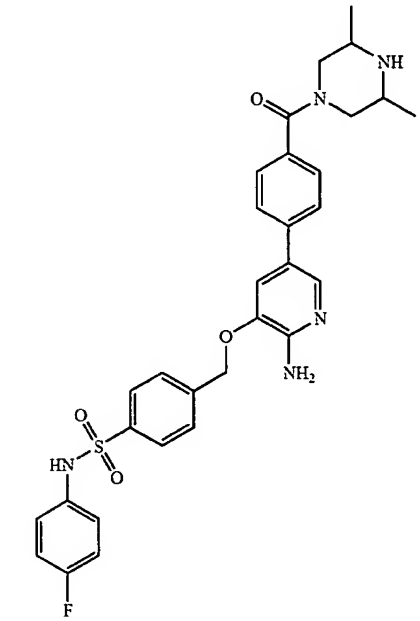


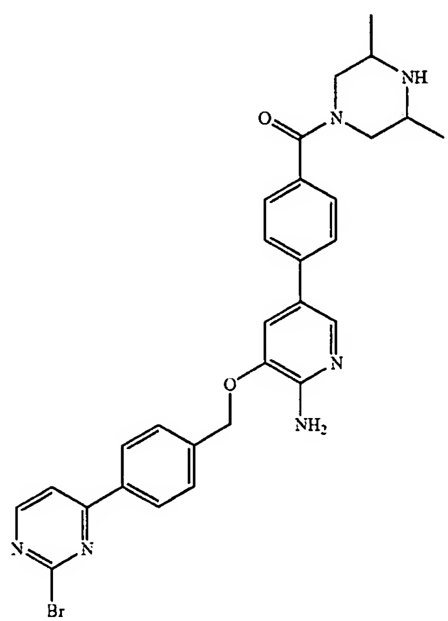
% Inhibition = 12



% Inhibition = 14

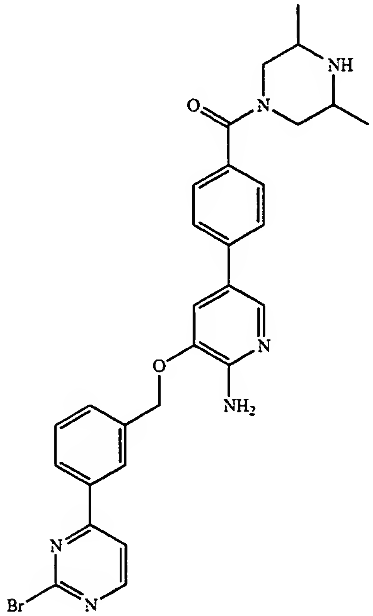


% Inhibition = 14

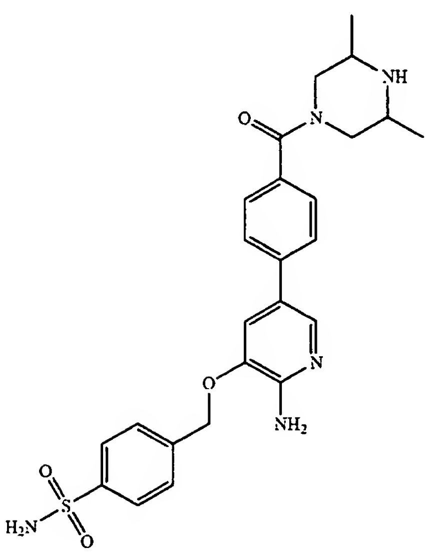


% Inhibition = 17

TABLE 8-continued

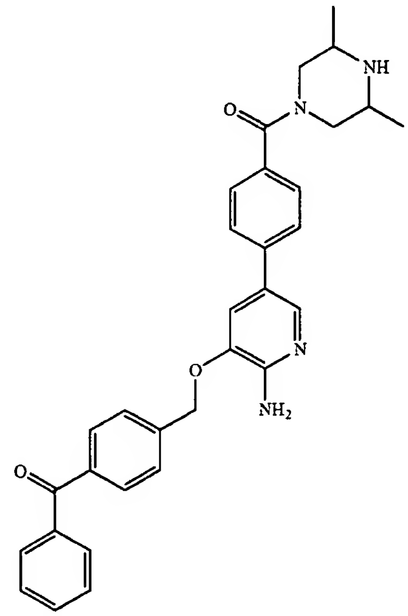


% Inhibition = 19

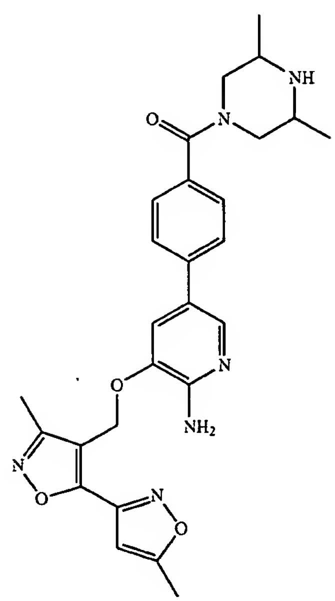


% Inhibition = 16

TABLE 8-continued

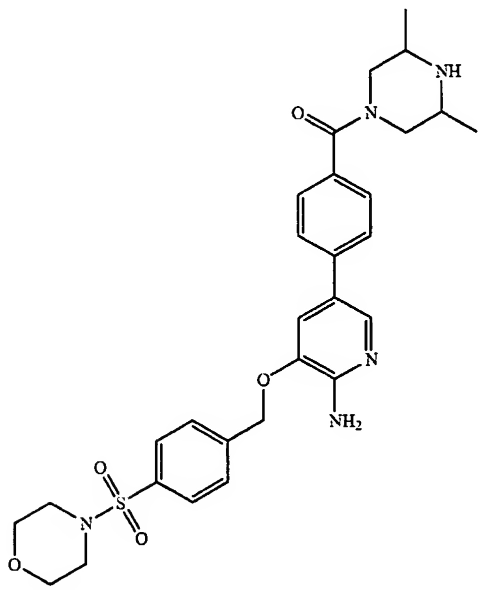


% Inhibition = 35



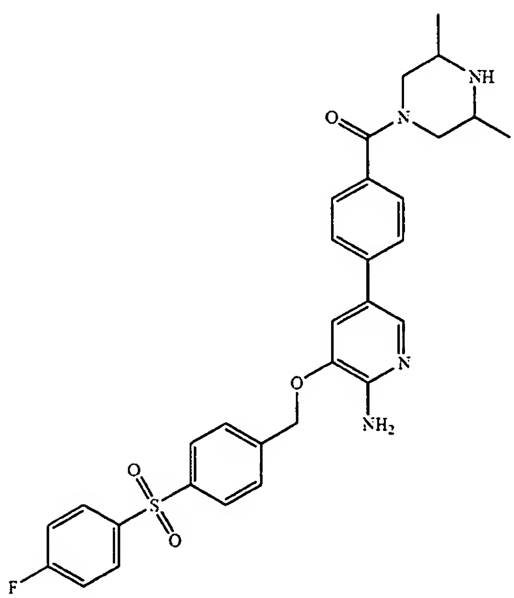
% Inhibition = 25

TABLE 8-continued



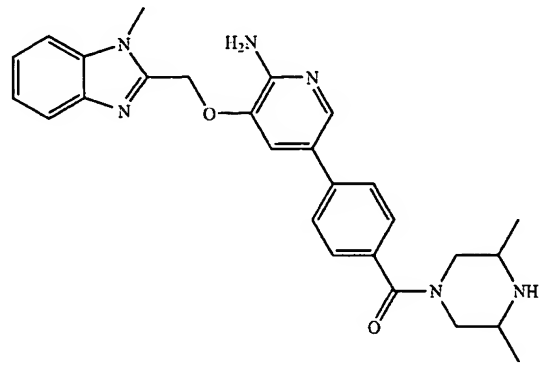
% Inhibition = 13

Section E: Examples L-613 to L-628



% Inhibition = 13

TABLE 8-continued



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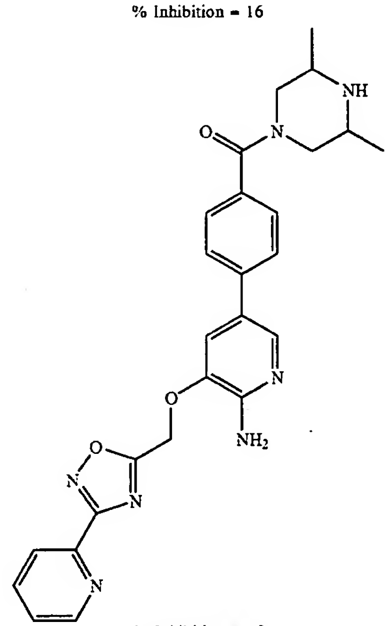
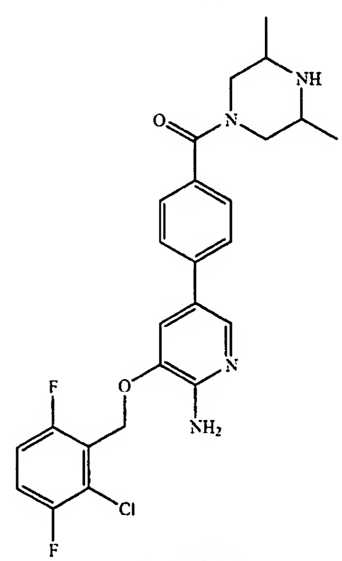
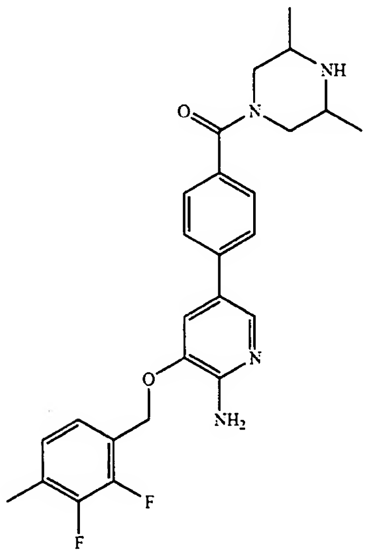


% Inhibition = 15

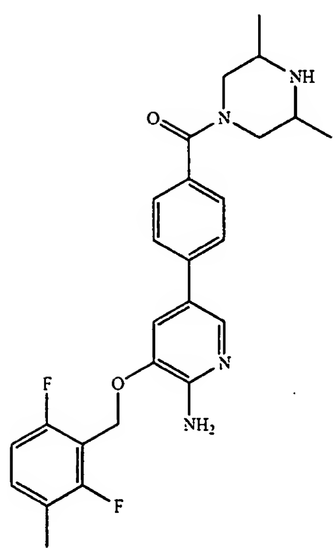


% Inhibition = 51

TABLE 8-continued

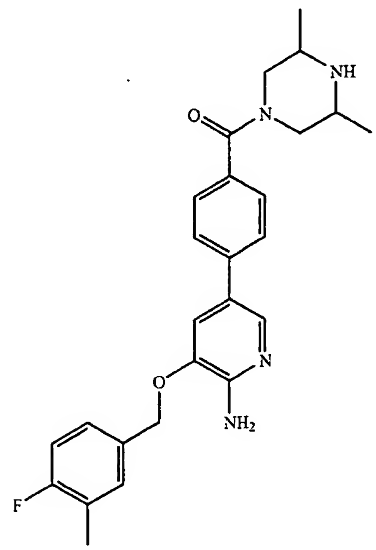


% Inhibition = 37

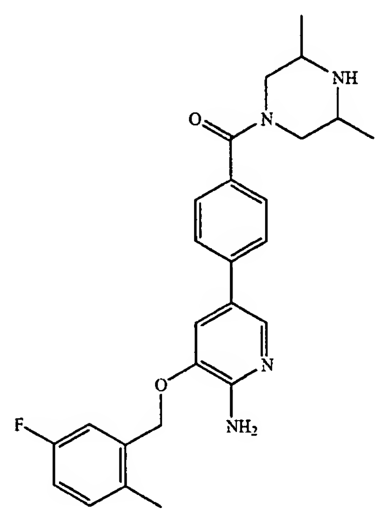


% Inhibition = 35

TABLE 8-continued

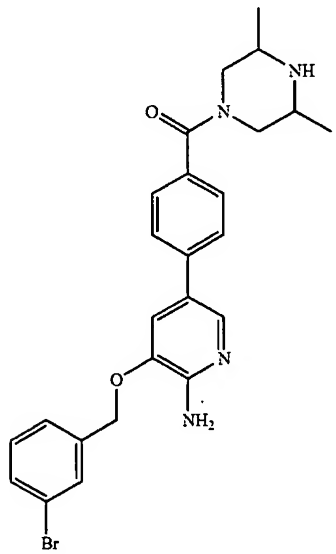


% Inhibition = 16

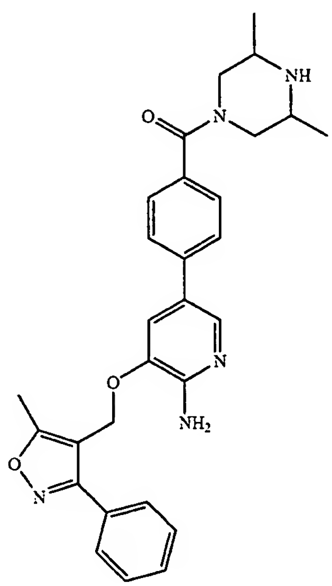


% Inhibition = 28

TABLE 8-continued

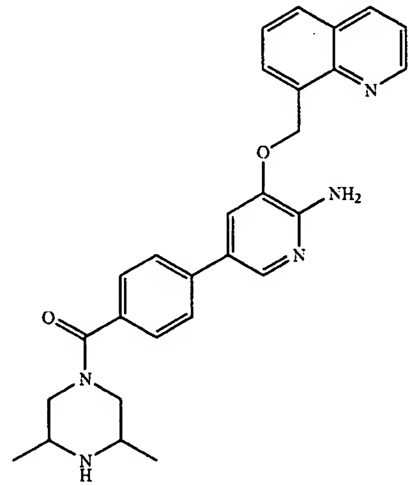


% Inhibition = 21

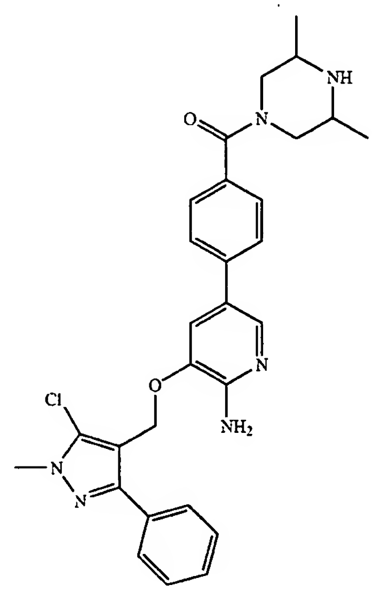


% Inhibition = 16

TABLE 8-continued

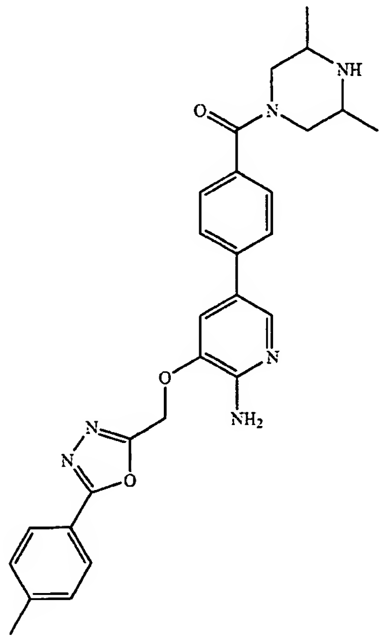


% Inhibition = 17

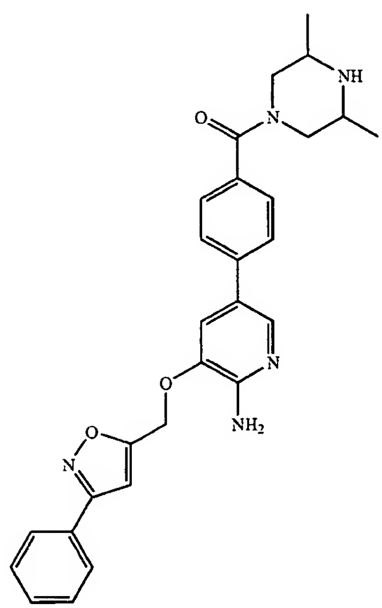


% Inhibition = 18

TABLE 8-continued

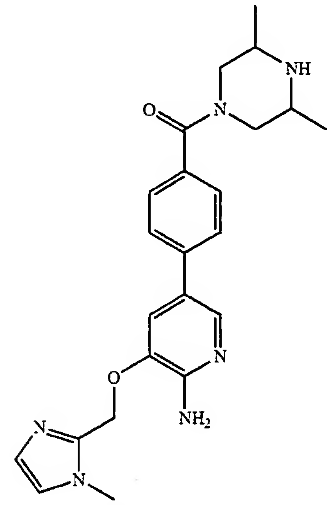


% Inhibition = 14

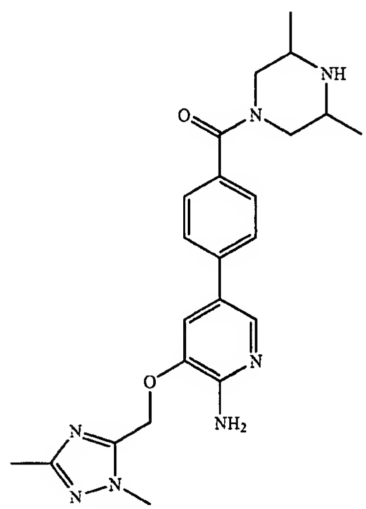


% Inhibition = 16

TABLE 8-continued

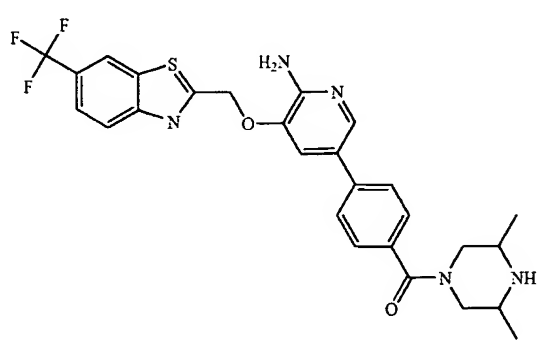


% Inhibition = 12



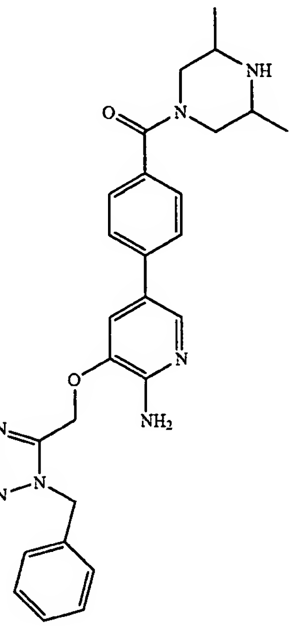
% Inhibition = 13

Section F: Examples L-629 to L-636

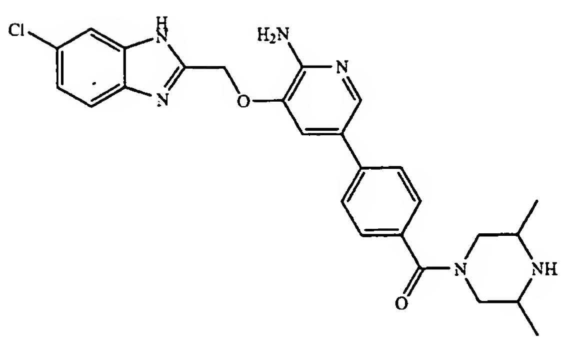


% Inhibition = 27

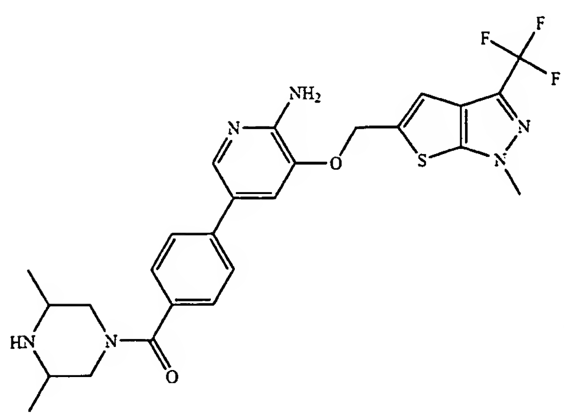
TABLE 8-continued



% Inhibition = 15

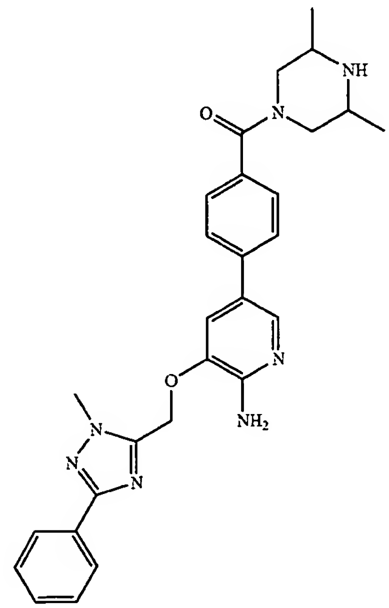


% Inhibition = 10

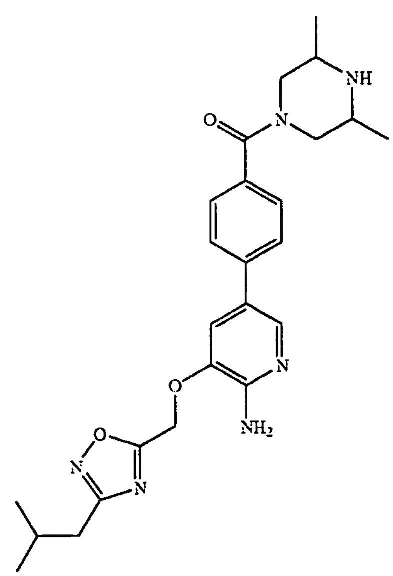


% Inhibition = 13

TABLE 8-continued

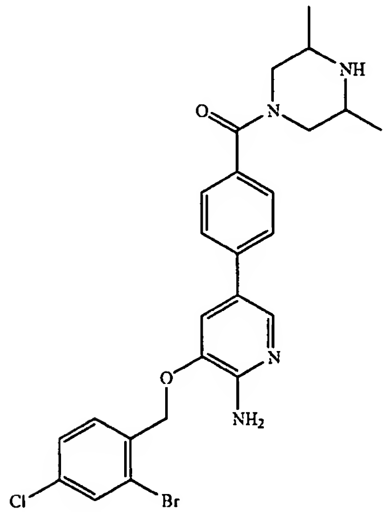


% Inhibition = 13

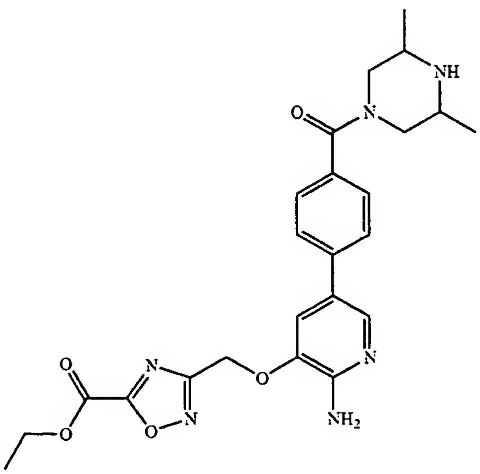


% Inhibition = 14

TABLE 8-continued



% Inhibition = 29



% Inhibition = 13

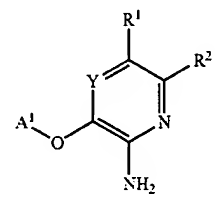
The present invention is not to be limited in scope by the exemplified aspects which are intended as illustrations of single aspects of the invention, and any clones, DNA or amino acid sequences which are functionally equivalent are within the scope of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

The disclosure of U.S. Provisional Application Ser. No. 60/449,588, filed Feb. 26, 2003, and U.S. Provisional Application Ser. No. 60/540,229, filed Jan. 29, 2004, are hereby incorporated by reference in their entireties.

All references cited herein are hereby incorporated by reference in their entireties.

We claim:

1. A compound of formula 1



1

wherein:

Y is CR^{12};

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, $—S(O)_mR^4$, $—SO_2NR^4R^5$, $—S(O)_2OR^4$, $—NO_2$, $—NR^4R^5$, $—(CR^6R^7)_nOR^4$, —CN, $—C(O)R^4$, $—OC(O)R^4$, $—O(CR^6R^7)_nR^4$, $—NR^4C(O)R^5$, $—(CR^6R^7)_nC(O)OR^4$, $—(CR^6R^7)_nNCR^4R^5$, $—C(=NR^6)NR^4R^5$, $—NR^4C(O)NR^5R^6$, $—NR^4S(O)_pR^5$ or $—C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, $—O—C_{1-12}$ alkyl, $—O—(CH_2)_nC_{3-12}$ cycloalkyl, $—O—(CH_2)_nC_{6-12}$ aryl, $—O—(CH_2)_n$(3–12 membered heteroalicyclic) or $—O—(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is $(CR^9R^{10})_n$-A^2

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl,

—$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —OC(O)R^4, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

R^{12} is hydrogen;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

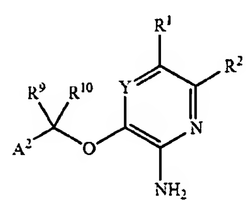
p is 1 or 2;

wherein said 3–12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5–12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine;

or a pharmaceutically acceptable salt, or hydrate thereof.

2. The compound of claim 1, wherein the compound has formula 1a

1a



wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

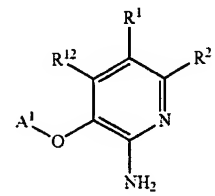
3. The compound of claim 2, wherein R^1 is selected from C_{6-12} aryl and 5–12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

4. The compound of claim 2, wherein A^2 is substituted by at least one halogen atom.

5. The compound of claim 1, wherein R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

6. A compound of formula 2

2



wherein:

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^2 is hydrogen;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12}-aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_nR^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_nC_{3-12}$ cycloalkyl, —O—$(CH_2)_nC_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

A^1 is —$(CR^9R^{10})_n$-A^2;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_mR^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_nOR^4$, —CN, —$C(O)R^4$, —OC(O)R^4, —$NR^4C(O)R^5$, —$(CR^6R^7)_nC(O)OR^4$, —$(CR^6R^7)_nNCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_pR^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to

form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_n C_{3-12}$ cycloalkyl, —O—$(CH_2)_n C_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

R^{12} is hydrogen;

m is 0, 1 or 2;

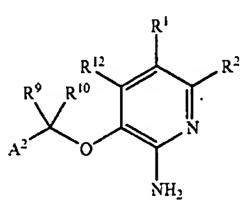
n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

wherein said 3–12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5–12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine;

or a pharmaceutically acceptable salt, or hydrate thereof.

7. The compound of claim 6, wherein the compound has formula 2a



2a

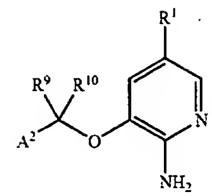
wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

8. The compound of claim 7, wherein R^1 is selected from C_{6-12} aryl and 5–12 membered heteroaryl, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

9. The compound of claim 7, wherein A^2 is substituted by at least one halogen atom.

10. The compound of claim 6, wherein R^1 is a furan, thiopene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, trithiane or phenyl group, and each hydrogen in R^1 is optionally substituted by one or more R^3 groups.

11. A compound of formula 4



4

wherein:

R^1 is selected from C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic; and each hydrogen in R^1 is optionally substituted by one or more R^3 groups;

R^3 is halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_m R^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_n OR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$O(CR^6R^7)_n R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_n C(O)OR^4$, —$(CR^6R^7)_n NCR^4R^5$, —$C(=NR^6)NR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_p R^5$ or —$C(O)NR^4R^5$, each hydrogen in R^3 is optionally substituted by one or more R^8 groups, and R^3 groups on adjacent atoms may combine to form a C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic group;

each R^4, R^5, R^6 and R^7 is independently hydrogen, halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl; or any two of R^4, R^5, R^6 and R^7 bound to the same nitrogen atom may, together with the nitrogen to which they are bound, be combined to form a 3 to 12 membered heteroalicyclic or 5–12 membered heteroaryl group optionally containing 1 to 3 additional heteroatoms selected from N, O, and S; or any two of R^4, R^5, R^6 and R^7 bound to the same carbon atom may be combined to form a C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic or 5–12 membered heteroaryl group; and each hydrogen in R^4, R^5, R^6 and R^7 is optionally substituted by one or more R^8 groups;

each R^8 is independently halogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —CN, —O—C_{1-12} alkyl, —O—$(CH_2)_n C_{3-12}$ cycloalkyl, —O—$(CH_2)_n C_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic) or —O—$(CH_2)_n$(5–12 membered heteroaryl); and each hydrogen in R^8 is optionally substituted by one or more R^{11} groups;

each R^9 and R^{10} is independently hydrogen, halogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —$S(O)_m R^4$, —$SO_2NR^4R^5$, —$S(O)_2OR^4$, —NO_2, —NR^4R^5, —$(CR^6R^7)_n OR^4$, —CN, —$C(O)R^4$, —$OC(O)R^4$, —$NR^4C(O)R^5$, —$(CR^6R^7)_n C(O)OR^4$, —$(CR^6R^7)_n NCR^4R^5$, —$NR^4C(O)NR^5R^6$, —$NR^4S(O)_p R^5$ or —$C(O)NR^4R^5$; R^9 and R^{10} may combine to form a C_{3-12} cycloalkyl, 3–12 membered heteroalicyclic, C_{6-12} aryl or 5–12 membered heteroaryl ring; and each hydrogen in R^9 and R^{10} is optionally substituted by one or more R^3 groups;

A^2 is C_{6-12} aryl, 5–12 membered heteroaryl, C_{3-12} cycloalkyl or 3–12 membered heteroalicyclic, and A^2 is optionally substituted by one or more R^3 groups;

each R^{11} is independently halogen, C_{1-12} alkyl, C_{1-12} alkoxy, C_{3-12} cycloalkyl, C_{6-12} aryl, 3–12 membered heteroalicyclic, 5–12 membered heteroaryl, —O—C_{1-12} alkyl, —O—$(CH_2)_n C_{3-12}$ cycloalkyl, —O—$(CH_2)_n C_{6-12}$ aryl, —O—$(CH_2)_n$(3–12 membered heteroalicyclic), —O—$(CH_2)_n$(5–12 membered heteroaryl) or —CN, and each hydrogen in R^{11} is optionally substituted by one or more groups selected from halogen, —OH, —CN, —C_{1-12} alkyl which may be partially or fully halogenated, —O—C_{1-12} alkyl which may be partially or fully halogenated, —CO, —SO and —SO_2;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4; and

p is 1 or 2;

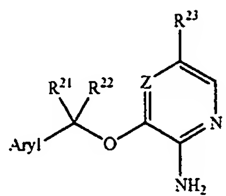
wherein said 3–12 membered heteroalicyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said 5–12 membered heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine;

or a pharmaceutically acceptable salt, or hydrate thereof.

12. The compound of claim 11, wherein A^2 is C_{6-12} aryl or 5–12 membered heteroaryl optionally substituted by one or more R^3 groups.

13. A compound of formula 6

6



wherein,

Z is CR or N;

Aryl is an optionally fused aryl or an optionally fused heteroaryl group which is optionally substituted by one or more substituents selected from the group consisting of a halogen, —OR^{24}, COR^{24}, —$COOR^{24}$, —$CONR^{24}R^{25}$, —CN, —NO_2, —$S(O)_mR^{24}$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, aryl, —$NR^{24}R^{25}$, —$NR^{24}C(O)R^{25}$ and —$NR^{24}S(O)_pR^{25}$;

R^{21} and R^{22} are independently selected from the group consisting of hydrogen, halogen, —COR^{24}, —$COOR^{24}$, —$CONR^{24}R^{25}$, —CN, perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, alkenyl, alkynyl, and aryl;

R^{23} is selected from the group consisting of:

an optionally fused aryl, heteroaryl, alicyclic or heterocyclic group, optionally substituted by one or more substituents selected from the group consisting of a halogen, —$(CH_2)_n$—OR^{24}, COR^{24}, —$COOR^{24}$, —$CONR^{24}R^{25}$, —CN, —NO_2, —$S(O)_mR^{24}$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, —O-perfluoroalkyl, lower alkyl, cycloalkyl, heterocycle, heteroaryl, alkenyl, alkynyl, aryl, —$(CH_2)_n$—$NR^{24}R^{25}$, —$NR^{24}C(O)R^{25}$ and —$NR^{24}S(O)_pR^{25}$, wherein said heterocycle, heteroaryl and aryl substituents may be optionally substituted by a group selected from the group consisting of lower alkyl, halogen, —$C(O)NR^{24}R^{25}$, $NR^{24}R^{25}$, $NR^{24}C(O)R^{25}$ and $NR^{24}S(O)_pR^{25}$;

—OR^{24}, —COR^{24}, —$COOR^{24}$, —CN, —NO_2, —$S(O)_m R^{24}$, —$SO_2NR^{24}R^{25}$, perfluoroalkyl, cycloalkyl, heterocycle, alkenyl, and alkynyl;

R^{24} and R^{25} are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aminoalkyl, alkylaminoalkyl, alkylaminocycloalkyl, dialkylaminoalkyl and —$(CH_2)_n$-heterocycle, wherein said —$(CH_2)_n$-heterocycle may be further substituted by one or more of lower alkyl, —$(CH_2)_n$-hydroxy, heterocycle and —$C(O)R^{26}$,

or R^{24} and R^{25} can combine to form a 5- to 6-membered heterocyclic ring having one or more heteroatoms selected from the group consisting of N, O, S, S(O) and SO_2, said 5- to 6-membered heterocyclic ring may be optionally substituted by lower alkyl, —$(CH_2)_n$-heterocycle, cycloalkyl, halo, —$(CH_2)_n$—$NR^{26}R^{27}$, amino, —$C(O)R^{26}$, —NR^{26}—$(O)OR^{27}$ and —NR^{26}—$C(O)R^{27}$;

wherein R^{26} and R^{27} are independently selected from the group consisting of hydrogen, lower alkyl, —$(CH_2)_n$-cycloalkyl and —C(O)—$(CH_2)_n$—OH;

except that when Z is N and R^{21} and R^{22} are H and Aryl is m-chlorophenyl, R^{23} is not piperazine;

m is 0, 1 or 2;

n is 0, 1, 2 or 3;

p is 1 or 2;

wherein said heterocyclic group is selected from pyrroline, pyrrolidine, dioxolane, imidazoline, imidazolidine, pyrazoline, pyrazolidine, pyran, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine and trithiane and said heteroaryl group is selected from furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, oxadiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine;

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13, wherein R^{23} is aryl or heteroaryl.

15. A compound selected from the group consisting of: (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}—N-(3-pyrrolidin-1-yl-propyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-amino-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone; (4-(6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-hydroxymethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-

[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-diethylamino-ethyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-(4-Hydroxy-piperidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-piperidin-1-yl-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-(cyclopropylmethyl-amino)-ethanesulfonic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-((R)-3-Hydroxy-pyrrolidin-1-yl)-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-cyclopropylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 2-diethylamino-ethanesulfonic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxyl]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-{4-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-3-morpholin-4-yl-propan-2-ol; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diethylamino-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-3-ylmethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-diisopropylamino-ethoxy)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(1-methyl-piperidin-4-yloxy)-phenyl]-pyridin-2-ylamine; N-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-[4-(1,1-dioxo-1lambda*6*-isothiazolidin-2-yl)-phenyl]-pyridin-2-ylamine; N-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-phenyl-pyridin-2-ylamine; N-(4-{6-amino-5-[(R)-1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-thiophen-3-yl-pyridin-2-ylamine; 5-benzo[b]thiophen-2-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 4-methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-

(2-morpholin-4-yl-ethyl)-urea; (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(1-methyl-piperidin-4-yl)-urea; (R)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; (S)-3-amino-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-(6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-hydroxy-ethyl)-urea; 4-methyl-piperazine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-urea; 1-(4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-3-(2-morpholin-4-yl-ethyl)-urea; (R)-2-pyrrolidin-1-ylmethyl-pyrrolidine-1-carboxylic acid (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-amide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide; 3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-amino-pyrrolidin-1-yl)-methanone; (3-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzoic acid; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-3-aminopyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-3-amino-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(1-methyl-piperidin-4-yl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-pyrrolidin-1-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(2-morpholin-4-yl-ethyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-pyrrolidin-1-yl-propyl)-benzamide; 4-{6-amino-5-[1-(3-fluoro-2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-N-(3-morpholin-4-yl-propyl)-benzamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-pyrazol-4-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-diisopropylamino-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[1-(2-morpholin-4-yl-ethyl)-1H-pyrazol-4-yl]-pyridin-2-ylamine; {4-[6-amino-5-(3-fluoro-2-methoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-fluoro-2-methoxy-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(3-fluoro-2-isopropoxy-benzyloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 5-(4-amino-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid methyl ester; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-acetic acid; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-ethanone; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-3-hydroxy-pyrrolidin-1-yl)-ethanone; 4-[2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy}-pyridin-3-yl}-phenoxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester; 2-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenoxy)-1-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-ethanone; {4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; N-{4-[6-amino-5-(3-fluoro-6,7,8,9-tetrahydro-5H-

benzocyclohepten-5-yloxy)-pyridin-3-yl]-phenyl}-methanesulfonamide; 3-(3-fluoro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yloxy)-5-(1H-pyrazol-4-yl)-pyridin-2-ylamine; 3-[1-(2-chloro-3-fluoro-phenyl)-ethoxy]-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyridin-2-ylamine; 5'-benzyloxy-[2,3']bipyridinyl-6'-ylamine; 5-benzyloxy-[3,3']bipyridinyl-6-ylamine; 3-benzyloxy-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-benzyloxy-[3,3']bipyridinyl-6,6'-diamine; 5'-(2-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 3-(2-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(4-chloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 3-(4-chloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(4-chloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(2-chloro-3,6-difluoro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,4']bipyridinyl-6-ylamine; 3-(2-chloro3,6-difluoro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2-chloro-3,6-difluoro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5'-(2,6-dichloro-benzyloxy)-[2,3']bipyridinyl-6'-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,4']bipyridinyl-6-ylamine; 3-(2,6-dichloro-benzyloxy)-5-pyrimidin-5-yl-pyridin-2-ylamine; 5-(2,6-dichloro-benzyloxy)-[3,3']bipyridinyl-6,6'-diamine; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6,6'-diamine; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-4-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; {6'-amino-5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-yl}-(4-methyl-piperazin-1-yl)-methanone; {6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4']bipyridinyl-2'-yl}-(4-methyl-piperazin-1-yl)-methanone; 5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine; 5'-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-6'-ylamine; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine; 3-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-5-pyrimidin-5-yl-pyridin-2-ylamine; {6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[2,3']bipyridinyl-5-yl}-(4-methyl-piperazin-1-yl)-methanone; 5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-[3,4]bipyridinyl-6-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 5-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-benzonitrile; 4-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperidin-4-ol; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperidin-1-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-pyrrolidin-1-yl-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-methyl-benzoic acid methyl ester; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(dimethyl-piperazin-1-ylmethyl)-phenyl]-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3,5-dimethoxy-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-fluoro-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-3-methyl-phenyl)-(dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-methyl-[1,4]diazepan-1-yl)-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-[1,4]diazepan-1-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-piperazin-1-yl-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-vinyl-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-methanone; 5-[(1-benzyl-pyrrolidin-3-ylamino)-methyl]-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N-azetidin-3-yl-benzamide; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-N,N-dimethyl-benzenesulfonamide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1H-benzoimidazol-2-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(6-methoxy-1-methyl-1H-benzoimidazol-2-yl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-(4-methyl-[1,4]diazepane-1-sulfonyl)-phenyl]-pyridin-2-ylamine; 6-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-1-methyl-1H-indazole-3-carboxylic acid amide; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-methyl-1H-pyrazol-4-yl)-pyridin-2-ylamine; 5-(3-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-3-methyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-fluoro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 5-benzo [1,3]dioxol-5-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenol; (3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol; 3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dichloro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethyl-phenyl)-pyridin-2-ylamine; 5-(5-chloro-2-methoxy-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 5-(3-chloro-4-fluoro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(5-

fluoro-2-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-isopropyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-benzonitrile; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-difluoro-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-ethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,4-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethyl-phenyl)-pyridin-2-ylamine; 5-(2-chloro-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-trifluoromethoxy-phenyl)-pyridin-2-ylamine; 1-(2-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-fluoro-phenyl)-pyridin-2-ylamine;(2-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanol; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-o-tolyl-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2-methoxy-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,6-dimethyl-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-morpholin-4-yl-methanone; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-chloro-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone; 4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-2-methyl-phenyl)-((3R,5S)-dimethyl-piperazin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-[4-((2R,6S)-2,6-dimethyl-morpholin-4-ylmethyl)-phenyl]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-morpholin-4-ylmethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-dimethyl-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-m-tolyl-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dimethoxy-phenyl)-pyridin-2-ylamine; 5-biphenyl-3-yl-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 5-(3,5-bis-trifluoromethyl-phenyl)-3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,4-dichloro-phenyl)-pyridin-2-ylamine; 1-(3-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-ethanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3,5-difluoro-phenyl)-pyridin-2-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(2,5-dichloro-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-4-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(3-ethoxy-phenyl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(3-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; 7-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-2-phenyl-4H-pyrido[3,2-b][1,4]oxazin-3-one; {4-[6-amino-5-(3-fluoro-2-trifluoromethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; (4-[6-amino-5-(2,6-difluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(3,5-dimethyl-piperazin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-3,6-difluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-ethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; 3-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester; 3-{2-amino-5-[4-(3,5-dimethyl-piperazine-1-carbonyl)-phenyl]-pyridin-3-yloxymethyl}-benzoic acid methyl ester; (4-[6-amino-5-(2-methyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; [4-(6-amino-5-cyclohexylmethoxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(3-hydroxy-phenyl)-ethyl]-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[2-(2,6-dichloro-phenyl)-ethyl]-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-(1-benzyl-piperidin-4-yl)-benzamide; 4-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-benzamide; (4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-ethyl-piperazin-1-yl)-methanone; {4-[6-amino-5-(2,6-dichloro-benzyloxy)-pyridin-3-yl]-phenyl}-(3,5-dimethyl-piperazin-1-yl)-methanone; (6-amino-3-aza-bicyclo [3.1.0]hex-3-yl)-(4-{6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-methanone; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-morpholin-4-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-(2-pyrrolidin-1-yl-ethyl)-1H-[3,3']bipyridinyl-6-one; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-6'-(2-pyrrolidin-1-yl-ethoxy)-[3,3']bipyridinyl-6-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-1H-[3,3']bipyridinyl-6-one; (4-{6-amino-5-[1-(2,4,6-trimethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-chloro-6-fluoro-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-fluoro-phenyl)-pyridin-2-ylamine; 6'-amino-5'-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-1H-[3,3']bipyridinyl-6-one; 5'-bromo-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-[3,3']bipyridinyl-6-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(4-dimethylamino-phenyl)-pyridin-2-ylamine; 5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-2'-methoxy-[3,3']bipyridinyl-6-ylamine; 3-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-5-(1H-indol-5-yl)-pyridin-2-ylamine; (4-{6-amino-5-[1-(2,6-dichloro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(3,5-dimethyl-piperazin-1-yl)-methanone; [4-(6-amino-5-benzyloxy-pyridin-3-yl)-phenyl]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-thiazol-2-yl-pyridin-2-ylamine; (4-{6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(2,6-dichloro-3-fluoro-benzyloxy)-5-(1-methyl-1H-imidazol-2-yl)-pyridin-2-ylamine; {4-[6-amino-5-(2,4,6-trimethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; {4-[6-amino-5-(2,3,5,6-tetramethyl-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-

piperidin-1-yl)-methanone; {4-[6-amino-5-(2,4,6-trifluoro-benzyloxy)-pyridin-3-yl]-phenyl}-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(2-fluoro-6-trifluoromethyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-methyl-nicotinamidine; 6-amino-5-[1-(2,6-dichloro-3-fluoro-phenyl)-ethoxy]-N-(2-morpholin-4-yl-ethyl)-nicotinamidine; (4-{6-amino-5-[1-(2,4,5-trifluoro-phenyl)-propoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; (4-{6-amino-5-[1-(6-chloro-2-fluoro-3-methyl-phenyl)-ethoxy]-pyridin-3-yl}-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 3-(1-{2-amino-5-[4-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-phenyl]-pyridin-3-yloxy}-ethyl)-benzoic acid; and pharmaceutically acceptable salts, and hydrates thereof.

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EXHIBIT B

COPY OF THE
MAINTENANCE FEE STATEMENT
FOR US PATENT NO. 7,230,098

1 PAGE

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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
7,230,098	$980.00	$0.00	11/22/10	10/786,610	06/12/07	02/26/04	04	NO	4050203

<u>EXHIBIT C</u>

COPY OF THE REQUEST FOR CERTIFICATE OF CORRECTION FOR US PATENT NO. 7,230,098 AS FILED ON SEPTEMBER 8, 2011

4 PAGES

Docket No.: PC23572A
CERTIFICATE OF CORRECTION
U.S. PATENT NO. 7,230,098

Certificate of Transmission (37 C.F.R. §1.8):

I hereby certify that this correspondence is being electronically transmitted via **EFS-Web** to the United States Patent and Trademark Office, **Certificate of Corrections Branch,** on this **8th** day of **September, 2011**.

/Christina M. Compelube/
Christina M. Compelube

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 7,230,098

Application No.: 10/786,610

Confirmation No.: 2828

Inventors: Jingrong Jean CUI et al.

Issue Date.: June 12, 2007

For: AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. § 254, and 37 C.F.R. § 1.322, this is a request for a Certificate of Correction in the above-identified patent. The mistakes identified in the appended Form occurred through the fault of the Patent Office, as clearly disclosed by the records of the application which matured into this patent.

The complete Certificate of Correction involves one (1) page. Issuance of the Certificate of Correction containing the correction is earnestly requested. Since these changes are necessitated through no fault of the Applicants, no fee is believed to be associated with this request. Nonetheless, should the Patent and Trademark Office determine that a fee is required, please charge all such fees to Deposit Account No. 16-1445.

Respectfully submitted,

Date: September 8, 2011

/Vincent P Liptak/
Vincent P. Liptak
Attorney for Applicants
Registration No. 53,225

Pfizer Inc.
Legal Division – Intellectual Property
10555 Science Center Drive
San Diego, California 92121
Phone: (858) 622-7908; Fax: (858) 678-8233

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,230,098

APPLICATION NO.: 10/786,610

ISSUE DATE : June 12, 2007

INVENTOR(S) : Jingrong Jean Cui, et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims, Claim 13, Column 1233, Line 46:

Please delete "CR" and insert -- CH --

In the Claims, Claim 13, Column 1233, Line 50:

Please delete "COR^{24}" and insert -- $-COR^{24}$ --

In the Claims, Claim 13, Column 1233, Line 64:

Please delete "COR^{24}" and insert -- $-COR^{24}$ --

In the Claims, Claim 13, Column 1234, Line 23:

Please delete "$-NR^{26}-(O)OR^{27}$" and insert -- $-NR^{26}-C(O)OR^{27}$ --

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Vincent P. Liptak
Legal Division – Patent Department
Pfizer Inc.
10555 Science Center Drive
San Diego, CA 92121

Electronic Acknowledgement Receipt

EFS ID:	10903645
Application Number:	10786610
International Application Number:	
Confirmation Number:	2828
Title of Invention:	AMINOHETEROARYL COMPOUNDS AS PROTEIN KINASE INHIBITORS
First Named Inventor/Applicant Name:	Jingrong Jean Cui
Customer Number:	22428
Filer:	Vincent P. Liptak/Christina Compelube
Filer Authorized By:	Vincent P. Liptak
Attorney Docket Number:	034536-1148
Receipt Date:	08-SEP-2011
Filing Date:	26-FEB-2004
Time Stamp:	14:27:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	PC23572ARequestForCorrection.pdf	54459 6917555f0271165d02b0f61d90843b9a327d510d	no	1

Warnings:

Information:

2	Request for Certificate of Correction	PC23572ACertofCorrectionFormSB44.pdf	69502 3ba7c38a6788c127f9936741cc5ce6e0ec4c1855	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	123961	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

EXHIBIT D

COPY OF THE FINAL NDA ACCELERATED APPROVAL LETTER FROM FDA

32 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202570

ACCELERATED APPROVAL

Pfizer Inc.
Attention: Ron C. Domingo, M.S., RAC
Manager
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Mr. Domingo:

Please refer to your New Drug Application (NDA) dated March 30, 2011, received March 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XALKORI® (crizotinib) Capsules, 200 mg and 250 mg.

We acknowledge receipt of your amendments dated January 4, 2011; February 22, 2011; February 24, 2011; March 31, 2011; April 13, 2011; April 15, 2011; April 26, 2011; May 3, 2011; May 19, 2011; May 24, 2011; May 26, 2011; June 6, 2011; June 8, 2011; June 9, 2011; June 13, 2011; June 14, 2011; June 15, 2011; June 17, 2011; June 23, 2011; June 24, 2011; June 30, 2011; July 1, 2011 (2); July 6, 2011; July 7, 2011; July 12, 2011; July 13, 2011 (2); July 15, 2011; July 21, 2011; July 22, 2011; July 26, 2011; July 27, 2011; August 1, 2011 (2); August 2, 2011(2); August 3, 2011; August 5, 2011; August 8, 2011; August 10, 2011; August 11, 2011; August 12, 2011; August 15, 2011; August 17, 2011; August 18, 2011; August 23, 2011 (2); August 24, 2011, and August 26, 2011.

This new drug application provides for the use of XALKORI (crizotinib) Capsules, 200 mg and 250 mg, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and required patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

Based on the stability data provided in your application, the drug product is granted a fifteen (15) month expiry as packaged in the proposed commercial configuration (60 count/HDPE bottle) when stored at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABELS

We acknowledge that your March 30, 2011, submission contains final printed container labels that will be used during the initial launch.

We note your agreement on August 3, 2011, and August 23, 2011, to revise your container labels at the next printing September 2011, to unbold and relocate the "Rx only" wording to the bottom of the label and to change the wording on the left side panel to read "Store at room temperature 20° to 25° C (68° to 77° F); excursions permitted between 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]". We acknowledge that your August 24, 2011, submission contains final printed container labels with these changes to be used at next printing.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for XALKORI (crizotinib) Capsules, 200 mg and 250 mg, was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. We remind you of your postmarketing requirement specified in your submission dated August 1, 2011. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by XALKORI (crizotinib) Capsules, 200 mg and 250 mg, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530(b), withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical trials to verify the clinical benefit of XALKORI (crizotinib) Capsules, 200 mg and 250 mg. These postmarketing trials are subject to the reporting requirements of 21 CFR 314.81. These requirements, along with required completion dates, are listed below.

1789-1

Clinical trial report and datasets from A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of PF-02341066 vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-2

Clinical trial report and datasets from A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

Final Protocol Submission:	06/2010 (submitted)
Trial Completion:	12/2015
Final Report Submission:	06/2016

Submit clinical protocols to your IND 73544, with a cross reference letter to this NDA. Submit all final reports to this NDA as supplemental applications. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s).**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of drug interactions caused by the induction of human CYP2B and CYP2C enzymes by XALKORI (crizotinib) Capsules, 200 mg and 250 mg.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1789-3

Submit the final report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.

The timetable you submitted on August 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2011
Study Completion:	12/2011
Final Report Submission:	12/2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of visual disorders with XALKORI (crizotinib) Capsules, 200 mg and 250 mg, and to assess signals of a serious risk of QT prolongation, drug-drug interactions with CYP3A inhibitors and inducers and gastric pH elevating drugs, and increased concentrations of XALKORI (crizotinib) Capsules, 200 mg and 250 mg in patients with hepatic impairment or severe renal impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1789-4

Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied. The following examinations should be performed in these patients at baseline, 2 and 6 weeks after drug administration and 2-8 weeks after discontinuation of the therapy (single visit post therapy).

1. Best corrected distance visual acuity
2. Refractive error associated with best corrected distance visual acuity
3. Pupil size under standardized lighting conditions
4. Slit lamp biomicroscopy of the anterior segment
5. Intraocular pressure
6. Ocular coherence tomography of the macula
7. Dilated fundus photography of the retina

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2011
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-5

Complete the ECG sub-study in trial A8081007 and submit the final report, along with a thorough review of cardiac safety data to address any potential impact of crizotinib on QTc interval prolongation in patients.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-6

Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inhibitor (*e.g.,* ketoconazole).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-7

Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inducer (*e.g.,* rifampin).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-8

Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	09/2011
Trial Completion:	07/2013
Final Report Submission:	01/2014

1789-9

Conduct a trial in humans to determine the appropriate crizotinib dose in patients with severe renal impairment.

The timetable you submitted on August 12, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	09/2011
Trial Completion:	04/2012
Final Report Submission:	10/2012

1789-10

Conduct a trial in humans to determine how to dose crizotinib with regard to gastric pH elevating agents (*i.e.*, a proton-pump inhibitor, an H2-receptor antagonist, and an antacid).

The timetable you submitted on August 11, 2011, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	01/2012
Trial Completion:	03/2013
Final Report Submission:	09/2013

Submit the protocols to your IND 073544, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1789-11

To assess the adequacy of the current cut-off, conduct a clinical trial to explore response to crizotinib in ALK-negative patients based on current assay cut-off. This should be compared to historic controls and to the response in ALK-positive patients. Additional biomarkers should be assessed in ALK-negative patients.

The timetable you submitted on August 24, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2011
Trial Completion:	05/2013
Final Report Submission:	11/2013

1789-12

To conduct exposure-response analysis for progression-free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081007 and to submit the analysis plan for review.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2009 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-13

To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081014 and to submit the analysis plan for review.

The timetable you submitted on August 3, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2010 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2015
Final Report Submission:	06/2016

Submit clinical protocols to your IND 073544 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.

XALKORI® (crizotinib) Capsules, oral
Initial U.S. Approval: August 2011

----------------------INDICATIONS AND USAGE----------------------
XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

----------------DOSAGE AND ADMINISTRATION----------------
- 250 mg taken orally twice daily with or without food. (2.1)
- Dosing interruption and/or dose reduction to 200 mg taken orally twice daily may be required based on individual safety and tolerability, then to 250 mg taken orally once daily if further reduction is necessary. (2.2)

----------------DOSAGE FORMS AND STRENGTHS----------------
- XALKORI Capsules: 250 mg and 200 mg. (3)

----------------------CONTRAINDICATIONS----------------------
- None (4)

----------------WARNINGS AND PRECAUTIONS----------------
- Pneumonitis: Severe, including fatal, treatment-related pneumonitis has been observed. Monitor patients for pulmonary symptoms indicative of pneumonitis. Permanently discontinue in patients diagnosed with treatment-related pneumonitis. (5.1)
- Hepatic Laboratory Abnormalities: Concurrent elevations in ALT and total bilirubin have occurred. Monitor monthly and as clinically indicated with more frequent testing in patients with Grade 2-4 elevations. Temporarily suspend, dose reduce, or permanently discontinue XALKORI as indicated. (5.2)
- QT Interval Prolongation: In patients who have a history of or predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms and electrolytes should be considered. (5.3)
- ALK Testing: Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI. (5.4)
- Pregnancy: XALKORI can cause fetal harm when administered to a pregnant woman. (5.5, 8.1)

----------------------ADVERSE REACTIONS----------------------
The most common adverse reactions (≥25%) are vision disorder, nausea, diarrhea, vomiting, edema, and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------------------DRUG INTERACTIONS----------------------
- CYP3A Inhibitors: Avoid concurrent use of XALKORI with strong CYP3A inhibitors. (7.1)
- CYP3A Inducers: Avoid concurrent use of XALKORI with strong CYP3A inducers. (7.2)
- CYP3A Substrates: Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Avoid concurrent use of XALKORI with CYP3A substrates with narrow therapeutic indices. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

XALKORI is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose and schedule of XALKORI is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole. XALKORI may be taken with or without food. If a dose of XALKORI is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

2.2 Dose Modification

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of XALKORI should be reduced to 200 mg taken orally twice daily. If further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily based on individual safety and tolerability. Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Tables 1 and 2.

Table 1: XALKORI Dose Modification – Hematologic Toxicities[a]

CTCAE[b] Grade	XALKORI Dosing
Grade 3	Withhold until recovery to Grade ≤2, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤2, then resume at 200 mg twice daily[c]

[a] Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] NCI Common Terminology Criteria for Adverse Events.
[c] In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg once daily. Permanently discontinue in case of Grade 4 recurrence.

Table 2: XALKORI Dose Modification – Non-Hematologic Toxicities

CTCAE Grade	XALKORI Dosing
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade ≤1 or baseline, then resume at 200 mg twice daily[a]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	Permanently discontinue
Any Grade pneumonitis[b]	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤1, then resume at 200 mg twice daily[a]
Grade 4 QTc prolongation	Permanently discontinue

[a] In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.
[b] Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

Complete blood counts including differential white blood cell counts should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. Liver function tests should be monitored monthly and as clinically indicated, with more frequent repeat testing if Grade 2, 3 or 4 abnormalities are observed.

3. DOSAGE FORMS AND STRENGTHS
250 mg capsules
Hard gelatin capsule, size 0, pink opaque cap and body, with "Pfizer" on the cap and "CRZ 250" on the body.

200 mg capsules
Hard gelatin capsule, size 1, white opaque body and pink opaque cap, with "Pfizer" on the cap and "CRZ 200" on the body.

4. CONTRAINDICATIONS
None

5. WARNINGS AND PRECAUTIONS

5.1 Pneumonitis
XALKORI has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other causes of pneumonitis should be excluded. XALKORI should be permanently discontinued in patients diagnosed with treatment-related pneumonitis *[see Dosage and Administration (2.2)]*.

5.2 Hepatic Laboratory Abnormalities
Grade 3 or 4 ALT elevation was observed in 7% of patients in Study A and in 4% of patients in Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 3 patients from Study A (2%) and 1 patient from Study B (less than 1%) required permanent discontinuation from treatment. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase were detected in 1/255 (less than 0.5%) of patients with available laboratory data across both studies. Liver function tests including ALT and total bilirubin should be monitored once a month and as clinically indicated, with more

frequent repeat testing for Grades 2, 3 or 4 elevation in patients who develop transaminase elevations *[see Dosage and Administration (2.2) and Adverse Reactions (6)].*

5.3 QT Interval Prolongation

QTc prolongation has been observed. XALKORI should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered. Permanently discontinue XALKORI in patients who develop Grade 4 QTc prolongation. Withhold XALKORI in patients who develop Grade 3 QTc prolongation until recovery to less than or equal to Grade 1, then resume XALKORI at 200 mg twice daily. In case of recurrence of Grade 3 QTc prolongation, withhold XALKORI until recovery to less than or equal to Grade 1, then resume XALKORI at 250 mg once daily. Permanently discontinue XALKORI if Grade 3 QTc prolongation recurs *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.4)].*

5.4 ALK Testing

Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with XALKORI *[see Clinical Studies (14)].*

Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Refer to an FDA-approved test's package insert for instructions on the identification of patients eligible for treatment with XALKORI.

5.5 Pregnancy

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. There are no adequate and well-controlled studies in pregnant women using XALKORI. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)].*

6. ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Studies A and B, patients with locally advanced or metastatic ALK-positive NSCLC received crizotinib 250 mg orally twice daily continuously. Among the 255 patients for whom data on Grade 1-4 adverse reactions are available, median exposure to study drug was 5.1 months in Study A and 7.8 months in Study B. Dosing interruptions occurred in 36% and 45% of patients in Studies A and B, and lasted greater than 2 weeks in 13% and 19% of patients in Studies A and B, respectively. Dose reductions occurred in 44% and 29% of patients in Studies A and B, respectively. The rates of treatment-related adverse events resulting in permanent discontinuation were 6% in Study A and 3% in Study B. The most common adverse reactions (≥25%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in at least 4% of patients in both studies included ALT increased and neutropenia.

Among the 397 patients for whom information on deaths and serious adverse reactions are available, deaths within 28 days of the last dose of study drug occurred in 45 patients. Ten (2.5%) patients died within 28 days of their first dose of study drug. Causes of death included disease progression (32 patients), respiratory events (9), and other (4). Respiratory causes of death included pneumonia (2), hypoxia (2), ARDS (1), dyspnea (1), pneumonitis (1), empyema (1), and pulmonary hemorrhage (1). Other causes of deaths included septic shock,

DIC, cardiovascular event, and death due to unknown cause (1 each). Serious adverse events in greater than or equal to 2% of patients included pneumonia, dyspnea, and pulmonary embolism.

Table 3 lists the common adverse reactions on Studies A and B in patients receiving XALKORI.

Table 3: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic ALK-Positive NSCLC on Studies A and B[1]

Adverse Event	Treatment Emergent N=255		Treatment Related N=255	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Eye Disorders				
Vision Disorder[2]	163 (64%)	0	159 (62%)	0
Gastrointestinal Disorders				
Nausea	145 (57%)	2 (<1%)	136 (53%)	0
Diarrhea	124 (49%)	1 (<1%)	109 (43%)	0
Vomiting	116 (45%)	3 (1%)	101 (40%)	0
Constipation	98 (38%)	2 (<1%)	69 (27%)	1 (<1%)
Esophageal Disorder[3]	51 (20%)	3 (1%)	29 (11%)	0
Abdominal Pain[4]	40 (16%)	1 (<1%)	20 (8%)	0
Stomatitis[5]	27 (11%)	1 (<1%)	15 (6%)	1 (<1%)
General Disorders				
Edema[6]	97 (38%)	2 (<1%)	72 (28%)	0
Fatigue	80 (31%)	6 (2%)	51 (20%)	4 (2%)
Chest Pain/Discomfort[7]	30 (12%)	1 (<1%)	3 (1%)	0
Fever	30 (12%)	1 (<1%)	2 (<1%)	0
Infections and Infestations				
Upper Respiratory Infection[8]	50 (20%)	1 (<1%)	4 (2%)	0
Investigations				
Alanine Aminotransferase Increased	38 (15%)	17 (7%)	34 (13%)	14 (5%)
Aspartate Aminotransferase Increased	29 (11%)	7 (3%)	24 (9%)	5 (2%)
Metabolism and Nutrition				
Decreased Appetite	69 (27%)	3 (1%)	49 (19%)	0
Musculoskeletal				
Arthralgia	29 (11%)	3 (1%)	4 (2%)	0
Back Pain	28 (11%)	0	2 (<1%)	0
Nervous System Disorders				
Dizziness[9]	60 (24%)	0	42 (16%)	0
Neuropathy[10]	58 (23%)	1 (<1%)	34 (13%)	1 (<1%)
Headache	34 (13%)	1 (<1%)	10 (4%)	0
Dysgeusia	33 (13%)	0	30 (12%)	0
Psychiatric Disorders				
Insomnia	30 (12%)	0	8 (3%)	0
Respiratory Disorders				
Dyspnea	57 (22%)	16 (6%)	5 (2%)	3 (1%)
Cough	54 (21%)	3 (1%)	9 (4%)	0
Skin Disorders				
Rash	41 (16%)	0	25 (10%)	0

[1]Study A used CTCAE v4.0, and Study B used CTCAE v3.0.
[2]Includes diplopia, photopsia, photophobia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.
[3]Includes dyspepsia, dysphagia, epigastric discomfort/pain/burning, esophagitis, esophageal obstruction/pain/spasm/ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.
[4]Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal tenderness.
[5]Includes mouth ulceration, glossodynia, glossitis, cheilitis, mucosal inflammation, oropharyngeal pain/discomfort, oral pain, and stomatitis.

[6]Includes edema, edema localized, and peripheral edema.
[7]Includes chest pain, chest discomfort, and musculoskeletal chest pain.
[8]Includes nasopharyngitis, rhinitis, pharyngitis, and upper respiratory tract infection.
[9]Includes balance disorder, dizziness, and presyncope.
[10]Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensory neuropathy.

Vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia were reported in 159 (62%) patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Caution should be exercised when driving or operating machinery by patients who experience vision disorder *[see Patient Counseling Information (17)].*

Neuropathy as defined in Table 3 and attributed to study drug by the investigator was reported in 34 (13%) patients. While most events were Grade 1, Grade 2 motor neuropathy and Grade 3 peripheral neuropathy were reported in 1 patient each. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grade 1 or 2 in severity.

Bradycardia has been reported in 12 (5%) patients treated with XALKORI. All of these cases were Grade 1 or 2 in severity.

Complex renal cysts have been reported in 2 (1%) patients treated with XALKORI. There were no reports of abnormal urinalyses or renal impairment in these cases.

Laboratory Abnormalities

Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were seen in 5.2%, 0.4%, and 11.4% of patients, respectively.

7. DRUG INTERACTIONS

7.1 Drugs That May Increase Crizotinib Plasma Concentrations

Coadministration of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations *[see Clinical Pharmacology (12.3)].* The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

7.2 Drugs That May Decrease Crizotinib Plasma Concentrations

Coadministration of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations *[see Clinical Pharmacology (12.3)].* The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort, should be avoided.

7.3 Drugs Whose Plasma Concentrations May Be Altered By Crizotinib

Crizotinib inhibits CYP3A both *in vitro* and *in vivo [see Clinical Pharmacology (12.3)].* Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, should be avoided.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D ***[see "Warnings and Precautions" (5.5)]***

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies of XALKORI in pregnant women. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. Crizotinib was administered to pregnant rats and rabbits during organogenesis to study the effects on embryo-fetal development. Postimplantation loss was increased at doses ≥ 50 mg/kg/day (approximately 1.2 times the AUC at the recommended human dose) in rats. No teratogenic effects were observed in rats at doses up to the maternally toxic dose of 200 mg/kg/day (approximately 5 times the AUC at the recommended human dose) or in rabbits at doses of up to 60 mg/kg/day (approximately 3 times the AUC at the recommended human dose), though fetal body weights were reduced at these doses.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. If this drug is used during pregnancy, or if the patient or their partner becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

It is not known whether XALKORI is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from XALKORI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of XALKORI in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 10 times the AUC in adult patients at the recommended human dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

Of the 119 patients in Study A, 16 (13%) were 65 years or older. Of the 136 patients in Study B, 19 (14%) were 65 years or older. No overall differences in safety or efficacy were observed in comparison with younger patients.

8.6 Hepatic Impairment

XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Clinical studies excluded patients with AST or ALT greater than 2.5 x ULN, or greater than 5 x ULN, if due to liver metastases. Patients with total bilirubin greater than 1.5 x ULN were also excluded. Treatment with XALKORI should be used with caution in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No starting dose adjustment is needed for patients with mild (creatinine clearance [CLcr] 60 to 90 mL/min) and moderate renal impairment (CLcr 30 to 60 mL/min), as steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr greater than 90 mL/min) in Study B. The potential need for starting dose adjustment in patients with severe renal impairment cannot be determined, as clinical and pharmacokinetic data were available for only one patient. In addition, no data are available for patients with end-stage renal disease. Therefore, caution should be used in patients with severe renal

impairment (CLcr less than 30 mL/min) or patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

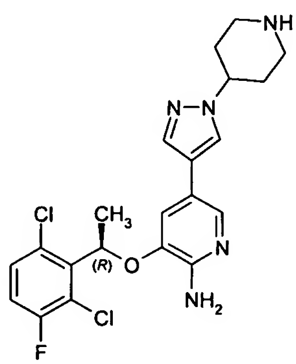
10. OVERDOSAGE

There have been no known cases of XALKORI overdose. Treatment of overdose with XALKORI should consist of general supportive measures. There is no antidote for XALKORI.

11. DESCRIPTION

XALKORI (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is $C_{21}H_{22}Cl_2FN_5O$. The molecular weight is 450.34 Daltons. Crizotinib is described chemically as (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine.

The chemical structure of crizotinib is shown below:



Crizotinib is a white to pale-yellow powder with a pKa of 9.4 (piperidinium cation) and 5.6 (pyridinium cation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

XALKORI capsules are supplied as printed hard-shell capsules containing 250 mg or 200 mg of crizotinib together with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients.

The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin, and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

12.3 Pharmacokinetics

Absorption
Following oral single-dose administration, crizotinib was absorbed with median time to achieve peak concentration of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady state systemic exposure (C_{min} and AUC) appeared to increase in a greater than dose proportional manner over the dose range of 200-300 mg twice daily.

The mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%) following the administration of a single 250 mg oral dose.

A high-fat meal reduced crizotinib AUC_{inf} and C_{max} by approximately 14%. XALKORI can be administered with or without food *[see Dosage and Administration (2.1)]*.

Distribution
The geometric mean volume of distribution (Vss) of crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins *in vitro* is 91% and is independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism
In vitro studies demonstrated that crizotinib is predominantly metabolized by CYP3A4/5. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites.

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

Elimination
Following single doses of crizotinib, the mean apparent plasma terminal half-life of crizotinib was 42 hours in patients.

Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/hr) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Drug Interactions
Coadministration of Crizotinib and CYP3A Substrates
Crizotinib inhibits CYP3A both *in vitro* and *in vivo*. Coadministration of crizotinib (250 mg twice daily for 28 days) in patients resulted in a geometric mean oral midazolam AUC that was 3.7-fold that observed when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A *[see Drug Interactions (7.3)]*.

Coadministration of Crizotinib and CYP3A Inhibitors
Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf}

and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. However, the magnitude of effect of CYP3A inhibitors on steady-state crizotinib exposure has not been evaluated *[see Drug Interactions (7.1)]*.

Coadministration of Crizotinib and CYP3A Inducers
Coadministration of a single 250 mg crizotinib dose with rifampin (600 mg QD), a strong CYP3A inducer, decreased crizotinib AUC_{inf} and C_{max} by 82% and 69%, respectively, compared to crizotinib alone. However, the effect of CYP3A inducers on steady-state crizotinib exposure has not been evaluated *[see Drug Interactions (7.2)]*.

Coadministration of Crizotinib and Antacids
The aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH (such as proton pump inhibitors, H_2 blockers, or antacids) may decrease the solubility of crizotinib and subsequently reduce its bioavailability. However, no formal studies have been conducted.

Coadministration With Other CYP Substrates
In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

An *in vitro* study in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of substrates for CYP1A2 or CYP3A.

Coadministration With Substrates of Transporters
Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered substrates of P-gp.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3 at therapeutic concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic uptake of substrates for these transporters.

Pharmacokinetics in Special Populations
Hepatic Impairment: As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. However, XALKORI has not been studied in patients with hepatic impairment. Clinical studies excluded patients with ALT or AST greater than 2.5 x ULN or greater than 5 x ULN if due to liver metastases. Patients with total bilirubin greater than 1.5 x ULN were also excluded *[see Use in Specific Populations (8.6)]*.

Renal Impairment: No dedicated renal impairment trial for XALKORI has been conducted. In Study B, steady-state trough concentrations in patients with mild (CLcr 60 to 90 mL/min, N=47) and moderate renal impairment (CLcr 30 to 60 mL/min, N=27) were similar to those in patients with normal renal function (CLcr greater than 90 mL/min, N=33). Limited data (N=1) are available in patients with severe renal impairment, and no data are available in patients with end-stage renal disease *[see Use in Specific Populations (8.7)]*.

Ethnicity: After 250 mg twice daily dosing, steady-state crizotinib C_{max} and AUC_τ in Asian patients were 1.57- and 1.50-fold those seen in non-Asian patients, respectively.

12.4 Cardiac Electrophysiology
The QT interval prolongation potential of crizotinib was assessed in all patients who received XALKORI 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Four of 308 patients (1.3%) were found to have QTcF (corrected QT by the Fridericia method) greater than or equal to 500 msec, and 10 of 289 patients (3.5%) had an increase from

baseline QTcF greater than or equal to 60 msec by automated machine-read evaluation of ECG. A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent increase in QTcF *[see Warnings and Precautions (5.3)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.

Crizotinib was genotoxic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cultures, in an *in vitro* human lymphocyte chromosome aberration assay, and in *in vivo* rat bone marrow micronucleus assays. Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given greater than or equal to 50 mg/kg/day for 28 days (greater than 3 times the AUC at the recommended human dose). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day (approximately 10 times the recommended human daily dose on a mg/m^2 basis) for 3 days.

14. CLINICAL STUDIES

The use of single-agent XALKORI in the treatment of locally advanced or metastatic ALK-positive NSCLC was investigated in 2 multi-center, single-arm studies (Studies A and B). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. In Study A, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received 250 mg of XALKORI orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.

Table 4: Demographic and Disease Characteristics in Studies A and B

Characteristics	Study A N=136	Study B N=119
Sex, n (%)		
Male	64 (47)	59 (50)
Female	72 (53)	60 (50)
Age (years)		
Median (range)	52 (29-82)	51 (21-79)
Race, n (%)		
White	87 (64)	74 (62)
Black	5 (4)	3 (3)
Asian	43 (32)	34 (29)
Other	1 (1)	8 (7)
ECOG PS at baseline, n (%)		
0	37 (27)	41 (35)
1	74 (54)	63 (53)
2 – 3[a]	25 (18)	15 (13)
Smoking status, n (%)		
Never smoked	92 (68)	86 (72)
Former smoker	39 (29)	32 (27)
Current smoker	5 (4)	1 (1)
Disease stage, n (%)		
Locally advanced	9 (7)	5 (4)
Metastatic	127 (93)	114 (96)
Histological classification, n (%)		
Adenocarcinoma	130 (96)	116 (98)
Large cell carcinoma	1 (1)	1 (1)
Squamous cell carcinoma	0	1 (1)
Adenosquamous carcinoma	3 (2)	0
Other	2 (2)	1 (1)
Prior systemic therapy for locally advanced or metastatic disease -- number of regimens, n (%)		
0	0	15 (13)
1	13 (10)	34 (29)
2	37 (27)	20 (17)
3	37 (27)	17 (14)
≥4	49 (36)	33 (28)

[a] Includes 1 patient with an ECOG PS of 1 at screening but was 3 at baseline.

One hundred thirty-six patients with locally advanced or metastatic ALK-positive NSCLC from Study A were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on investigator assessments, there was 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

One hundred nineteen patients with locally advanced or metastatic ALK-positive NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Efficacy data from Studies A and B are provided in Table 5.

Table 5: Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results from Studies A and B[a]

Efficacy Parameter	Study A N=136	Study B N=119
ORR (CR+PR)[b] [% (95% CI)]	50% (42%, 59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response[c] [Median (range) weeks]	41.9 (6.1+, 42.1+)	48.1 (4.1+, 76.6+)

[a]Response as assessed by the Investigator.
[b]One patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.
[c]Preliminary estimate using Kaplan-Meier method.
+Censored values

16. HOW SUPPLIED/STORAGE AND HANDLING

250 mg capsules
Hard gelatin capsule with pink opaque cap and body, printed with black ink "Pfizer" on the cap, "CRZ 250" on the body; available in:
Bottles of 60 capsules: NDC 0069-8140-20

200 mg capsules
Hard gelatin capsule with pink opaque cap and white opaque body, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body; available in:
Bottles of 60 capsules: NDC 0069-8141-20

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17. PATIENT COUNSELING INFORMATION

See 17.7 for FDA-Approved Patient Labeling.

17.1 Gastrointestinal Effects

Patients should be informed that nausea, diarrhea, vomiting, and constipation were the most commonly reported gastrointestinal adverse events occurring in patients who received XALKORI. Supportive care for gastrointestinal adverse events requiring treatment may include standard anti-emetic and/or anti-diarrheal or laxative medications *[see Adverse Reactions (6)]*.

17.2 Visual Effects

Patients should be informed that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters were commonly reported adverse events. These events began most commonly during the first two weeks of treatment. Patients should be advised to report flashes or floaters to their physicians *[see Adverse Reactions (6)]*.

17.3 Effects on Ability to Drive and Use Machines

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking XALKORI *[see Adverse Reactions (6)]*.

17.4 Concomitant Medications

Patients should be advised to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.

17.5 Instructions for Taking XALKORI

Patients should be advised to take XALKORI exactly as prescribed, not to change their dose or to stop taking XALKORI unless they are told to do so by their doctor. XALKORI may be taken with or without food. XALKORI capsules should be swallowed whole.

Patients should be instructed to keep XALKORI in the original container. Patients should not crush, dissolve, or open capsules.

Patients should avoid grapefruit or grapefruit juice while taking XALKORI.

If a patient misses a dose, the patient should be advised to take it as soon as they remember unless it is less than 6 hours until the next dose, in which case they should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

17.6 Pregnancy and Nursing

Patients of childbearing potential must be told to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Patients should be advised to inform their doctor if they or their partners are pregnant or think they may be pregnant. Patients should also be advised not to breastfeed while taking XALKORI.

17.7 FDA-Approved Patient Labeling

LAB-0440-2.0

PATIENT INFORMATION

XALKORI® (zal-KOR-ee) (crizotinib) Capsules

Read this patient information leaflet before you start taking XALKORI and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your condition or treatment.

What is the most important for me to know about XALKORI?

XALKORI may cause serious side effects, such as:

Swelling of the lungs (pneumonitis) - XALKORI may cause life-threatening swelling (inflammation) of the lungs during treatment. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- cough with or without mucous
- fever

Liver problems - Your doctor should do blood tests every month to check your liver while you are taking XALKORI. Tell your doctor right away if you get any of the following:

- your skin or the whites of your eyes turn yellow
- you feel tired
- your urine turns dark or brown (tea color)
- you have nausea or vomiting
- you have a decreased appetite
- you have pain on the right side of your stomach
- you bleed or bruise more easily than normal

See "What are possible side effects of XALKORI?" for more information about side effects.

What is XALKORI?

XALKORI is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that is advanced or that has spread to other parts of the body and is caused by a defect in a gene called ALK (anaplastic lymphoma kinase).

It is not known if XALKORI is safe and effective in children.

What should I tell my doctor before taking XALKORI?

Before you take XALKORI, tell your doctor if you:

- have heart problems, including a condition called long QT syndrome
- have liver or kidney problems
- have any other medical conditions
- are pregnant, or plan to become pregnant. XALKORI may harm your unborn baby.
    - Women who are able to become pregnant and men who take XALKORI should use birth control during treatment and for 3 months after stopping XALKORI.
    - Talk to your doctor about the birth control methods that may be right for you.
    - If you or your partner becomes pregnant, tell your doctor right away.
- are breastfeeding or plan to breastfeed. It is not known if XALKORI passes into your breast milk. You and your doctor should decide if you will take XALKORI or breastfeed. You should not do both.

Tell your doctor about the medicines you take, including prescription medicines, non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- St. John's Wort (Hypericum perforatum)

- Medicines for:
  - depression (antidepressants)
  - fungal infections (antifungals)
  - bacterial infections (antibiotics)
  - tuberculosis (TB)
  - HIV-AIDS
  - heart conditions
  - seizures

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take XALKORI?

- Take XALKORI exactly as your doctor tells you.
- Swallow XALKORI capsules whole.
- Do not crush, dissolve, or open capsules.
- You may take XALKORI with or without food.
- Do not change your dose or stop XALKORI unless your doctor tells you.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose (within 6 hours), just take your next dose at your regular time.
- Do not take more than 1 dose of XALKORI at a time.
- Call your doctor right away if you take too much XALKORI.
- Your doctor will check your blood and heart while you are taking XALKORI.

What should I avoid while taking XALKORI?

- You should not drink grapefruit juice or eat grapefruit during your treatment with XALKORI. It may make the amount of XALKORI in your blood increase to a harmful level.
- XALKORI can cause changes in your vision, dizziness, and tiredness. If you have these symptoms, use caution when driving a car, using machinery, or doing anything that needs you to be alert.

What are the possible side effects of XALKORI?

XALKORI may cause serious side effects:

- **See "What is most important for me to know about XALKORI?"**
- Changes in your heartbeat (called QT interval prolongation), very fast or abnormal heartbeats. Your doctor may check your heart during treatment with XALKORI. Tell your doctor right away if you have abnormal heartbeats, feel dizzy, or faint. These may be symptoms related to QT interval prolongation.

The most common side effects of XALKORI include:

- Vision problems
- These problems usually happen within 2 weeks of starting XALKORI. Tell your doctor right away if you have any change in vision, such as:
  - flashes of light
  - blurred vision
  - light hurting your eyes
  - new or increased floaters
- nausea
- diarrhea
- vomiting
- swelling of your hands and feet
- constipation

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of XALKORI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store XALKORI?

Store XALKORI at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep XALKORI in the original container, and keep the container closed tightly.
- Do not touch or handle crushed or broken XALKORI capsules. XALKORI is made with a capsule to prevent contact with the active ingredient.

Keep XALKORI and all medicines out of the reach of children.

General information about XALKORI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XALKORI for a condition for which it was not prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them.

This leaflet provides the most important information about XALKORI. If you would like to know more about XALKORI talk with your doctor. You can ask your doctor or pharmacist for more information about XALKORI.

For more information, go to www.XALKORI.com.

What are the ingredients in XALKORI?

Active ingredient: crizotinib.

Inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate.

Pink opaque capsule shell contains: gelatin, titanium dioxide, and red iron oxide.

White opaque capsule shell contains: gelatin and titanium dioxide.

Printing ink contains: shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

This Patient Information has been approved by the U.S. Food and Drug Administration

Distributed by:	Manufactured by:
Pfizer Labs Division of Pfizer Inc New York, NY 10017	Pfizer Ireland Pharmaceuticals Dublin, Ireland

LAB-0441-1.0
Revised: August 2011

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 200 mg crizotinib.

Manufactured by
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Pfizer

Pfizer

NDC 0069-8141-20
Rx only

XALKORI™
(crizotinib) **capsules**

200 mg

60 Capsules

FPO: UPC 80% x 5.5 mm
N 3 0069-8141-20 8

4151

Distributed by Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND
000000000

FPO

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE

See accompanying prescribing information.

Each capsule contains 250 mg crizotinib.

Manufactured by
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Pfizer

Pfizer

NDC 0069-8140-20
Rx only

XALKORI™

(crizotinib) capsules

250 mg

60 Capsules

FPO: UPC 80% x 5.5 mm
N 3 0069-8140-20 1

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FPO

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 200 mg crizotinib.

Manufactured by
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Pfizer

Pfizer NDC 0069-8141-20

XALKORI®

(crizotinib) capsules

200 mg

60 Capsules Rx only

FPO: UPC 80% x 5.5 mm
N 3 0069-8141-20 8

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Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND
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FPO

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight containers (USP).

DOSAGE AND USE
See accompanying prescribing information.

Each capsule contains 250 mg crizotinib.

Manufactured by
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Pfizer

Pfizer

NDC 0069-8140-20

XALKORI®

(crizotinib) **capsules**

250 mg

60 Capsules

Rx only

FPO: UPC 80% x 5.5 mm

N 3 0069-8140-20 1

4152

Distributed by Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
MADE IN IRELAND

000000000

FPO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
08/26/2011

EXHIBIT E

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES TABLE

19 PAGES

EXHIBIT E

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY REVIEW PERIOD FOR XALKORI™

Date	Activity	Comments
12/12/2005	Submission to FDA	IND 73,544 filed. Protocol No. A8081001 filed.
12/22/2005	Letter from FDA	To communicate that FDA confirmed receipt of IND 73,544. IND 73,544 became effective on January 21, 2006.
1/9/2006	Submission to FDA	Response to FDA Comments on for Protocol No. A8081001.
1/9/2006	Letter from FDA	To communicate clinical comments on the IND for PF-02341066 (c-met/HGFR inhibitor) protocol A8081001.
1/11/2006	Letter from FDA	To communicate that FDA accepted Pfizer's response to the clinical deficiencies noted in IND 73,544 (PF-02341066, c-Met/HGFR inhibitor).
1/12/2006	Submission to FDA	Notification of change in contact person.
1/26/2006	Submission to FDA	Protocol No. A8081001 amendment.
4/11/2006	Submission to FDA	IND information amendment - Pharmacology-Toxicology (120-Day Update)
8/28/2006	Submission to FDA	Protocol No. A8081001 amendment.
9/15/2006	Submission to FDA	Protocol No. A8081001 amendment.
9/28/2006	Submission to FDA	Protocol No. A8081001 amendment.
11/9/2006	Submission to FDA	Protocol No. A8081001 amendment.
1/10/2007	Submission to FDA	Annual Report pursuant to 21 C.F.R. 312.33
5/1/2007	Submission to FDA	Protocol No. A8081001 amendment.
5/8/2007	Submission to FDA	Protocol No. A8081001 amendment.
11/1/2007	Submission to FDA	Protocol No. A8081001 amendment (To convey that EML4-ALK has been identified as a driver in the etiology of a subset of NSCLCs and that the eligibility criteria have been modified to allow patients with lung cancers on study)
12/17/2007	Submission to FDA	Protocol No. A8081001 amendment.

Date	Activity	Comments
1/30/2008	Submission to FDA	IND Information Amendment (Updated Investigator's Brochure pursuant to 21 CFR 312.31)
1/31/2008	Submission to FDA	Protocol No. A8081001 amendment.
2/20/2008	Submission to FDA	Annual Report pursuant to 21 C.F.R. 312.33
3/20/2008	Submission to FDA	Protocol No. A8081001 amendment.
4/4/2008	Submission to FDA	Protocol No. A8081001 amendment.
5/8/2008	Submission to FDA	Protocol No. A8081001 amendment.
5/20/2008	Submission to FDA	Protocol No. A8081001 amendment.
7/16/2008	Submission to FDA	Protocol No. A8081001 amendment.
9/4/2008	Submission to FDA	Protocol No. A8081001 amendment.
10/2/2008	Submission to FDA	Protocol No. A8081001 amendment.
10/27/2008	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls in relation to Protocol No. A8081001
12/8/2008	Submission to FDA	Annual Report pursuant to 21 C.F.R. 312.33
3/2/2009	Submission to FDA	General Correspondence - Request for a Type A Meeting for PF-02341066 NSCLC Program
3/5/2009	Submission to FDA	IND Safety Report - 15-Day Initial Safety Report
3/19/2009	Email from FDA	Confirmation from FDA regarding Type B meeting for c-Met/ALK in NSCLC
3/19/2009	Submission to FDA	Protocol No. A8081001 amendment.
3/26/2009	Submission to FDA	General Correspondence - Briefing Package for Type B End-of-Phase 1 meeting for PF-02341066 NSCLC Program
4/15/2009	Email from FDA	Responses to Pfizer questions in the briefing document for the Type B meeting scheduled on April 23, 2009 for PF-02341066 NSCLC Program.
4/23/2009	Meeting with FDA	To convey high level meeting outcomes from the Type B meeting on April 23, 2009 for PF-02341066 NSCLC Program.
4/29/2009	Submission to FDA	General Correspondence - Authorization Letter for FDA to Cross Reference IND 73,544 while reviewing COG protocol ADVL0912 (Non-Pfizer sponsored clinical trial)

Date	Activity	Comments
5/22/2009	Email from FDA	To convey official FDA meeting minutes from the Type B meeting on April 23, 2009 for PF-02341066 NSCLC Program.
5/28/2009	Submission to FDA	General Correspondence - Request for Special Protocol Assessment (SPA) for global Phase 3 Protocol No. A8081007 (Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 Versus Standard of Care Chemotherapy (Premexetred or Docetaxel) in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus)
5/28/2009	Submission to FDA	General Correspondence - Request for QT-IRT Review based on the briefing package for the Type B meeting held on 4/23/2009
6/08/2009	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls in relation to Protocol No. A8081001
6/12/2009	Telecon with FDA	To convey official minutes from the FDA conference call regarding a Pfizer request for the "Real Time Review" of the PF-02341066 Pre-Investigational Device Exemption (IDE) package
6/16/2009	Email from FDA	To convey a request for additional information regarding development plans for the FISH-based ALK diagnostic test to be used in connection with Protocol No. A8081007
6/25/2009	Submission to FDA	New Protocol No. A8081002 (Phase 1/2 Open-Label Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Erlotinib with or without PF-02341066 in Patients with Advanced Non-Small Cell Adenocarcinoma of the Lung)
6/29/2009	Email from FDA	To confirm the date of the working Pre-IDE meeting with FDA (OIVD/CDRH, Diagnostic Division) regarding the diagnostic kit for determining patient eligibility for PF-02341066 (c-Met/ALK inhibitor) registrational and supportive studies in NSCLC.
7/1/2009	Submission to FDA	Protocol No. A8081001 amendment.
7/2/2009	Submission to FDA	New Protocol No. A8081008 (A Phase I Relative Bioavailability Study To Compare The Powder-In-Capsule and Immediate Release Tablet of PF-02341066 In Healthy Volunteers)
7/3/2009	Submission to FDA	General Correspondence – Response to FDA Request for Information on 6/16/2009 regarding Vysis ALK BreakApart FISH Probe Kit Commercial Test Development Plan
7/16/2009	Email from FDA	To acknowledge receipt of the Special Protocol Assessment (SPA) feedback and QT-IRT review from FDA for PF-02341066 (c-Met/ALK inhibitor) registrational study Protocol No. A8081007
7/20/2009	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls in relation to Protocol No. A8081008

Date	Activity	Comments
7/24/2009	Meeting with FDA	To convey draft high level results from the working Pre-IDE meeting with FDA (OIVD/CDRH, Diagnostic Division) regarding the assay for determining patient eligibility for PF-02341066 (c-Met/ALK inhibitor) registrational and supportive studies in NSCLC.
7/29/2009	Submission to FDA	Protocol No. A8081008 and No. A8081001 amendment.
7/31/2009	Submission to FDA	Protocol No. A8081001 amendment.
8/12/2009	Letter from FDA	To convey no agreement to SPA request of May 29, 2009 for Protocol No. A8081007
8/13/2009	Email from FDA	To convey FDA's edits to the draft minutes from the Pre-IDE meeting with OIVD, FDA Diagnostic Division, regarding the assay for determining patient eligibility for PF-02341066 (c-Met/ALK inhibitor) registrational and supportive studies in NSCLC.
8/13/2009	Email from FDA	To convey FDA's feedback regarding the Pre-IDE submission to OIVD, FDA Diagnostic Division. The assay will be used for determining patient eligibility for PF-02341066 (c-Met/ALK inhibitor) registrational and supportive studies in NSCLC.
8/28/2009	Submission to FDA	General Correspondence - Submission Transferred to eCTD Format (IND 73,544)
9/9/2009	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls
9/10/2009	Email from FDA	To record Pfizer and Abbott's responses to the FDA OIVD (Diagnostic Division) Pre-IDE memorandum for the PF-02341066 project (c-Met/ALK inhibitor).
9/11/2009	Submission to FDA	General Correspondence - Response to Special Protocol Assessment Comments for Protocol No. A8081007
9/11/2009	Submission to FDA	Protocol No. A8081007 amendment
9/11/2009	Submission to FDA	New Protocol No. A8081005 (Phase 2, Open-Label Single Arm Study of the Efficacy and Safety of Pf-02341066 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus)
9/18/2009	Submission to FDA	IND Safety Report Protocol No. A8081001
10/6/2009	Submission to FDA	Protocol No. A8081005 amendment.
10/8/2009	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls (Labeling)
10/9/2009	Submission to FDA	Protocol No. A8081002 amendment.
10/15/2009	Submission to FDA	Protocol No. A8081007 amendment.

Date	Activity	Comments
11/5/2009	Email from FDA	Notification that Abbott Molecular submitted the Investigational Device Exemption (IDE) for the FISH probe kit as a companion diagnostic for PF--02341066 (c-Met/ALK).
11/12/2009	Submission to FDA	Protocol # A808 (1008-1001) amendment.
11/25/2009	Submission to FDA	IND Safety Report Protocol No. A8081001
12/9/2009	Submission to FDA	Protocol No. A8081007 amendment.
12/11/2009	Email from FDA	Notification that the FDA approved the Investigational Device Exemption (IDE) application for the FISH probe kit that will be used to select patients for PF-02341066 (ALK/c-Met) clinical trials.
12/16/2009	Submission to FDA	New Protocol No. A8081006 (A Phase 1, Open-Label, Dose Escalation Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of Combined Oral C-Met/ALK Inhibitor (PF-02341066) and Pan-Her Inhibitor (PF-00299804) in Patients With Advanced Non-Small Cell Lung Cancer)
1/7/2010	Submission to FDA	Protocol No. A8081005 amendment.
1/7/2010	Submission to FDA	Protocol No. A8081002, No. A8081005 and No. A8081007 amendment.
1/8/2010	Submission to FDA	General Correspondence - Request for a Type B Meeting for PF-02341066 NSCLC Program.
1/11/2010	Submission to FDA	Annual Report pursuant to 21 C.F.R. 312.33
1/14/2010	Submission to FDA	Information Amendment Protocol No. A8081007 - Provided in this submission is the final and approved Statistical Analysis Plan.
1/27/2010	Submission to FDA	Safety Report for COG Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial)
2/2/2010	Submission to FDA	Protocol No. A8081002, No. A8081005 and No. A8081007 amendment
2/12/2010	Submission to FDA	New Protocol No. A8081009 (A Phase One Open-Label Single-Radiolabeled Dose Study To Investigate The Absorption, Metabolism And Excretion Of [^{14}C]PF-02341066 In Healthy Male Volunteers)
2/18/2010	Submission to FDA	Protocol No. A8081007 amendment
2/18/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
2/19/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
3/2/2010	Submission to FDA	Protocol No. A8081005 and No. A8081007 amendment
3/12/2010	Submission to FDA	General Correspondence - Briefing Package for Type B Meeting for PF-02341066 NSCLC Program

Date	Activity	Comments
3/12/2010	Submission to FDA	General Correspondence – Autorization for FDA to Cross Reference Pfizer IND 73,544 on behalf of Yael P Mosse, M.D. for his IND submission
3/17/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
3/19/2010	Submission to FDA	IND Safety Report Protocol No. A8081002
3/22/2010	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls
3/24/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
3/29/2010	Submission to FDA	Protocol No. A8081001, No. A8081005, No. A8081007 and No. A8081009 amendment.
4/6/2010	Submission to FDA	IND Safety Report Protocol No. A8081002
4/13/2010	Submission to FDA	New Protocol No. A8081013 (Phase 1B Open-Label Study Of The Safety and Clinical Activity Of Crizotinib (PF-02341066) In Tumors With Genetic Events Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus)
4/13/2010	Submission to FDA	Protocol No. A8081001 amendment
4/14/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
4/14/2010	Email from FDA	To convey high level FDA meeting minutes regarding crizotinibs (PF-02341066) agreement on accelerated approval for 2nd-line treatment of ALK-positive NSCLC, and the Phase 3 study design for the 1st-line treatment of ALK-positive NSCLC.
4/22/2010	Email from FDA	To accept a proposal to submit 7-day expedited reports to the IND electronically instead of via facsimile.
4/22/2010	Submission to FDA	Protocol No. A8081001, No. A8081002, No. A8081005 and No. A8081007 amendment
4/26/2010	Submission to FDA	New Protocol No. A8081018 (A Study In Trained Taste Panel Healthy Adult Volunteers To Investigate The Palatability Of Select Formulations Of Crizotinib Oral Liquid)
4/28/2010	Email from FDA	To convey official FDA meeting minutes regarding crizotinibs (PF-02341066) agreement on accelerated approval for 2nd-line treatment of ALK-positive NSCLC, and the Phase 3 study design for the 1st-line treatment of ALK-positive NSCLC.
5/7/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
5/11/2010	Meeting with FDA	To convey the high level meeting minutes with FDA/CDRH regarding the Abbott Molecular (AM) companion diagnostic to crizotinib (PF-02341066).
5/12/2010	Submission to FDA	Protocol No. A8081007 amendment

Date	Activity	Comments
5/17/2010	Submission to FDA	Protocol No. A8081001 amendment
5/17/2010	Submission to FDA	Request for Type B Pre-NDA Meeting for NSCLC Indication
5/19/2010	Submission to FDA	IND Safety Report – Compassionate Use
5/21/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
5/25/2010	Submission to FDA	IND Safety Report ADVL0912 (Non Pfizer Sponsored Clinical Trial)
5/27/2010	Submission to FDA	Protocol No. A8081018 amendment
6/1/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/7/2010	Submission to FDA	Protocol No. A8081007 amendment
6/7/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/7/2010	Submission to FDA	IND Information Amendment - Chemistry, Manufacturing, and Controls (Formulation - pediatric dosage form)
6/10/2010	Submission to FDA	General Correspondence - Information Amendment – Clinical Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/15/2010	Submission to FDA	General Correspondence – Autorization for FDA to Cross Reference Pfizer IND 73,544 on behalf of Ranee Mehra, MD and Hossein Borghaei, DO for their IND submission
6/15/2010	Submission to FDA	New Protocol No. A8081014 (Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of Crizotinib Versus Emetrexed/Cisplatin Or Pemetrexed/Carboplatin In Previously Untreated Patients With Non-Squamous Carcinoma Of The Lung Harboring A Translocation Or Inversion Event Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus)
6/15/2010	Submission to FDA	New Protocol No. A8081015 (A Phase 1, Fixed Sequence, Cross-Over Study To Estimate The Effect Of Multiple Doses Of Ketoconazole On The Single Dose Pharmacokinetics Of Crizotinib (PF- 02341066) In Healthy Volunteers)
6/15/2010	Submission to FDA	New Protocol No. A8081016 (A Phase 1, Fixed Sequence, Cross-Over Study To Estimate The Effect Of Multiple Dose Rifampin On The Single Dose Pharmacokinetics Of Crizotinib (PF-02341066) In Healthy Volunteers)
6/15/2010	Submission to FDA	General Correspondence - Information Amendment – Clinical Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/16/2010	Submission to FDA	Protocol No. A8081001 amendment
6/17/2010	Submission to FDA	Request for Type B Clinical Pharmacology Meeting for PF-02341066

Date	Activity	Comments
6/17/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/18/2010	Email from FDA	FDA granted a pre-NDA meeting date of July 29, 2010 to discuss the content and format of the NDA for crizotinib (PF-02341066) for the treatment of ALK-positive non-small cell lung cancer.
6/21/2010	Submission to FDA	General Correspondence - Briefing Package for Pre-NDA Type B Meeting for Crizotinib (PF-02341066) NSCLC Program
6/23/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
6/24/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
6/24/2010	Submission to FDA	New Protocol No. A8081011 (A Phase 1, Single Dose Bioequivalence and Food Effect Study in Healthy Volunteers Comparing the Commercial Image Capsules to the Immediate Release Tablets and Powder in Capsule Formulations Of Crizotinib (PF-02341066), and The Commercial Image Capsule in the Fasted to Fed State)
6/28/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non Pfizer Sponsored Clinical Trial)
6/30/2010	Submission to FDA	Protocol No. A8081001, No. A8081002, No. A8081005 and No. A8081007 amendment.
7/2/2010	Submission to FDA	IND Safety Report Protocol No. A8081005 and Protocol No. ADVL0912 (Non-Pfizer Sponsored Interventional Study)
7/7/2010	Submission to FDA	IND Safety Report Protocol No. A8081005 and Protocol No. A8081001
7/8/2010	Submission to FDA	New Protocol No. A8081010 (A Phase 1, Single Dose, Randomized, Cross-Over Absolute Bioavailability Study in Healthy Volunteers Comparing Oral to Intravenous Administration of Crizotinib (PF-02341066))
7/12/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Robert Goldsby, MD for his IND submission
7/14/2010	Submission to FDA	IND Safety Report Protocol No. A8081005, Protocol No. A8081001, and Protocol No. ADVL0912 (Non-Pfizer Sponsored Interventional Study)
7/14/2010	Submission to FDA	Protocol No. A8081005 and No. A8081007 amendment
7/16/2010	Submission to FDA	Request for Type B CMC Meeting
7/16/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Ranee Mehra, MD for his IND submission

Date	Activity	Comments
7/19/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Tobias Neff, MD for his IND submission
7/21/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial)
7/22/2010	Telecon with FDA	To convey discussion with Dr. Young from the Division of Scientific Investigations (DSI) regarding the future scheduling of site inspections involving crizotinib.
7/23/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
7/28/2010	Submission to FDA	IND Information Amendment - Clinical - Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial)
7/28/2010	Submission to FDA	IND Information Amendment - Clinical to inform the Agency of potentially drug-related pneumonitis with crizotinib (PF-02341066)
7/29/2010	Meeting with FDA	To convey outcome of the pre-NDA meeting for crizotinib (PF-02341066)
7/30/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
7/30/2010	Submission to FDA	IND Safety Report Protocol No. A8081001 and Protocol No. A8081005
8/3/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial)
8/5/2010	Submission to FDA	IND Safety Report Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial) and Protocol No. A8081005
8/6/2010	Submission to FDA	General Correspondence – Briefing Package for Clinical Pharmacology Type B Meeting
8/9/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Samuel Volchenboum, MD, PhD for his IND submission
8/11/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
8/12/2010	Submission to FDA	Protocol No. A8081001, No. A8081005, No. A8081007 and No. A8081010 amendment
8/16/2010	Submission to FDA	General Correspondence - Request for Proprietary Name Review
8/16/2010	Submission to FDA	IND Safety Report Protocol No. A8081001 and Protocol No. A8081005
8/17/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Kostas Arnaoutakis, MD, for his IND submission

Date	Activity	Comments
8/18/2010	Submission to FDA	IND Safety Report Protocol No. A8081007 and Protocol No. A8081001
8/19/2010	Submission to FDA	General Correspondence – Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Geoffrey Shapiro, M.D., Ph.D., for his IND submission
8/25/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
8/27/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
8/30/2010	Email from FDA	Request made by the Division of Scientific Investigations (DSI) within FDA to submit information which will assist them in administering the BIMO (Bioresearch Monitoring) program.
8/30/2010	Email from FDA	FDA sent the official minutes of the pre-NDA meeting for crizotinib that occurred on July 29, 2010.
8/31/2010	Email from FDA	FDA requested information regarding safety reports of neutropenia and pneumonitis in patients who have received crizotinib.
8/31/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
9/2/2010	Email from FDA	To convey FDA's internal meeting minutes regarding the Clinical Pharmacology meeting scheduled for September 8, 2010.
9/2/2010	Submission to FDA	Protocol No. A8081006 amendment
9/2/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Brian A. Van Tine, MD, Ph.D. for his IND submission
9/3/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
9/8/2010	Submission to FDA	General Correspondence - Response to FDA request for information on safety reports of neutropenia and pneumonitis made on August 31, 2010.
9/9/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
9/9/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Scott Gettinger MD, for his IND submission
9/13/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Timothy P. Cripe, M.D., Ph.D., for his IND submission
9/14/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
9/16/2010	Submission to FDA	IND Information Amendment - Clinical (Updated Investigator's Brochure)
9/22/2010	Submission to FDA	Information Amendment - CMC

Date	Activity	Comments
9/23/2010	Submission to FDA	IND Safety Report Protocol No. A8081005 and Protocol No. A8081001
9/24/2010	Submission to FDA	General Correspondence - Pfizer submitted a briefing package for the Type B, CMC pre-NDA meeting scheduled for October 29, 2010
9/24/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
9/28/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Ravi Salgia MD for his IND submission
9/28/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Ian Churchill Anderson MD for his IND submission
9/29/2010	Submission to FDA	IND Safety Report Protocol No. A8081005 and Protocol No. ADVL0912 (Non-Pfizer sponsored clinical trial)
9/30/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Faye M. Johnson, M.D., PhD. for her IND submission
10/1/2010	Submission to FDA	General Correspondence - Change in External Data Monitoring Committee Membership Protocol No. A8081007 and Protocol No. A8081005.
10/6/2010	Letter from FDA	To convey FDA's decision to grant crizotinib orphan-drug designation for the treatment of ALK-positive non-small cell lung cancer.
10/6/2010	Submission to FDA	General Correspondence - Dr. Herbst - Cross Referencing of IND (Change in treating physician)
10/7/2010	Submission to FDA	General Correspondece - Dr. Adkins - Cross Referencing of IND (Change in treating physician)
10/7/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
10/8/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Julie Brahmer MD, for her IND submission
10/12/2010	Submission to FDA	General Correspondence - Clinical Pharmacology, Internal Meeting Minutes
10/12/2010	Submission to FDA	IND Information Amendment - Clinical - Protocol No. A8081006 amendment (Change In Protocol)
10/13/2010	Submission to FDA	IND Safety Report Protocol No. SPECIAL ACCESS PROGRAMME and Protocol No. A8081001

Date	Activity	Comments
10/13/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of James Strauss, M.D., for his IND submission
10/13/2010	Submission to FDA	General Correspondence - Official Pre-NDA Meeting Minutes
10/15/2010	Submission to FDA	General Correspondence - Dr. Janeway - Cross Referencing of IND (Change in treating physician)
10/18/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Douglas Hawkins, MD, for his IND submission
10/21/2010	Submission to FDA	IND Safety Report Protocol No. A8081001, Protocol No. A8081005 and Protocol No. A8081007
10/25/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Lawrence Einhorn, MD, for his IND submission
10/29/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Robert J. Hayashi, MD, for his IND submission
10/29/2010	Submission to FDA	IND Safety Report Protocol No. A8081007
10/29/2010	Meeting with FDA	To convey draft CMC meeting minutes with FDA regarding crizotinib (PF-02341066) to align expectations on development strategies and CMC plans in preparation for the NDA.
11/3/2010	Submission to FDA	IND Safety Report Protocol No. A8081001 IND Safety Report Special Access Programme and IND Safety Report A8081005
11/3/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Mark R. Hutchins, MD, for his IND submission
11/4/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Max Rabinowitz, M.D. for his IND submission
11/8/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. Douglas Adkins for his IND submission
11/10/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. James Strauss for his IND submission
11/10/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
11/12/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Alice Shaw, M.D., Ph.D. for her IND submission

Date	Activity	Comments
11/17/2010	Submission to FDA	IND Safety Report Protocol No. A8081007
11/19/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
11/19/2010	Submission to FDA	IND Safety Report Protocol No. A8081007
11/22/2010	General Correspondence - Request for Joint Pre-Approval Inspection	This correspondence is being sent to the attention of the crizotinib ONDQA project manager, Don Henry, to request a joint pre-approval inspection (PAI) for crizotinib and another Pfizer investigational product, axitinib (AG-013736).
11/23/2010	General Correspondence	This letter serves to authorize the Office of In Vitro Diagnostics (OIVD) on behalf of Karen Bijwaard to access Pfizer's IND 73,544. In addition, an authorization letter from Abbott Molecular Diagnostics (AMD) will allow the Center of Drugs Evaluation and Research to access AMD's IDE (G090233) for the Vysis ALK Break Apart FISH Probe Kit. Pfizer is formally collaborating with Abbott on Studies A8081005, A8081007, and A8081014. We request that all information in this IND be treated as confidential and that no information in the file beyond Studies A8081005, A8081007, and A8081014 be shared with AMD without the written consent of Pfizer.
11/23/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
11/24/2010	Submission to FDA	IND Safety Report Protocol No. A8081007
11/29/2010	Letter from FDA	Official Pre-NDA CMC meeting minutes
11/30/2010	Submission to FDA	IND Safety Report Protocol No. A8081005
11/30/2010	Submission to FDA	IND Safety Report Protocol No. A8081007
12/7/2010	Email from FDA	Crizotinib Fast Track and Rolling Submission Granted
12/7/2010	Submission to FDA	General Correpsondence - FDA CMC Meeting (Type B or A) Briefing Package – Meeting request
12/9/2010	Submission to FDA	Manufacturer's No. Report 2010158332 Initial 2010147407 Follow-up #3
12/10/2010	Submission to FDA	This 7-day expedited safety report will also be provided to the Division via facsimile. Manufacturer's No. Report 2010164276 Initial
12/14/2010	Submission to FDA	Protocol No. A8081014 amendment
12/14/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Leora Horn, MD for her IND submission

Date	Activity	Comments
12/14/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Jill Gilbert, MD for her IND submission
12/15/2010	Submission to FDA	Protocol No. A8081002 amendment
12/15/2010	Submission to FDA	Protocol No. A8081014 amendment
12/16/2010	Submission to FDA	IND Safety Report Protocol No. A8081001
12/20/2010	Submission to FDA	Manufacturer's No. Report: 2010158332 Follow-up, 2010130919 Follow-up, 2010121220 Follow-up, 2010141716 Follow-up, 2010147407 Follow-up
12/20/2010	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Mansoor N. Saleh, M.D. for his IND submission
12/22/2010	Submission to FDA	Manufacturer's No. Report 2010169641 Initial
12/24/2010	Submission to FDA	General Correspondence - Meeting Minutes from CMC Development Plan Meeting with FDA on October 29, 2010
12/24/2010	Submission to FDA	General Correspondence - Meeting Request Granted (Acceptance of response to request on July 16, 2010 for Type B Meeting Request)
12/28/2010	Submission to FDA	Manufacturer's No. Report 2010108765 Follow-up #2 2010141716 Follow-up #2
12/29/2010	Submission to FDA	Manufacturer's No. Report 2010173938 Initial 2010173209 Initial 15-Day
1/4/2011	Submission to FDA	Information Amendment - Clinical (Updated Investigator's Brochure)
1/4/2011	Submission to FDA	NDA 202570 – First wave
1/5/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Mansoor N. Saleh, M.D. for his IND submission
1/6/2011	Submission to FDA	Manufacturer's No. Report 2010178827 Initial, 2010158332 Follow-up #2, 2010121220 Follow-up #2, 2010147407 Follow-up #5, 2010173938 Follow-up #1
1/6/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Balazs Halmos, M.D. for his IND submission
1/7/2011	Submission to FDA	IND Information Amendment - Clinical (Updated Investigator's Brochure)

Date	Activity	Comments
1/7/2011	Submission to FDA	Manufacturer's No. Report 2010172122 Initial
1/11/2011	Submission to FDA	Manufacturer's No. Report 2010181394 Initial
1/12/2011	Email from FDA	To convey FDA acceptance of Pfizer proposal for 120-day safety update
1/18/2011	Submission to FDA	Manufacturer's No. Report 2010172122 Follow-up #1 2011002428 Initial
1/20/2011	Submission to FDA	Protocol No. A8081014 amendment
1/20/2011	Submission to FDA	Protocol No. A8081013 amendment
1/20/2011	Submission to FDA	Manufacturer's No. Report 2010181394 Follow-up #1 2010141716 Follow-up #3
1/24/2011	Submission to FDA	General Correspondence - Updated Data Monitoring Committee Charter for Protocol No. A8081007
1/25/2011	Submission to FDA	Manufacturer's No. Report 2011013757 Initial
1/25/2011	Submission to FDA	IND Safety Report AER #2010158332, 2010178827, 2010173938, 2011002428
1/25/2011	Submission to FDA	Protocol No. A8081005 amendment
1/25/2011	Submission to FDA	Protocol No. A8081007 amendment
1/26/2011	Submission to FDA	Manufacturer's No. Report 2011013757 Initial
1/31/2011	Submission to FDA	Manufacturer's No. Report 2011013757 Follow-up #2
2/1/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr.Pennell, MD for his IND submission
2/3/2011	Submission to FDA	Protocol No. A8081006 amendment
2/7/2011	Submission to FDA	IND Information Amendment - CMC
2/7/2011	Submission to FDA	Initial Safety Reports 2010172122
2/9/2011	Submission to FDA	Manufacturer's No. Report 2011019373 Initial
2/11/2011	Submission to FDA	Manufacturer's No. Report 2011013757 Follow-up #3
2/11/2011	Submission to FDA	New Protocol No. A8081019 (A Phase 1, Open-Label, Single Dose, Randomized, Cross-Over Relative Bioavailability Study Comparing an Oral Liquid Formulation to a Formulated Capsule of Crizotinib (Pf-02341066) in Healthy Volunteers)

Date	Activity	Comments
2/11/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Jennifer Carney, MD for her IND submission
2/11/2011	Submission to FDA	General Correspondence - CMC Follow-up Meeting, Internal Meeting Minutes
2/11/2011	Submission to FDA	Manufacturer's No. Report 2011026947 Initial
2/14/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. Wakelee, MD for his IND submission
2/15/2011	Submission to FDA	Manufacturer's No. Report 2011022304 Initial, 2011022308 Initial, 2010169641 Follow-up, 2011002428 Follow-up
2/18/2011	Submission to FDA	Manufacturer's No. Report 2011019373 Follow-up #1 2011026947 Follow-up #1
2/22/2011	Submission to FDA	NDA 202570 – Rationale for Plan and Priority Review and Accelerated Approval
2/24/2011	Submission to FDA	NDA 202570 – Second wave
2/25/2011	Submission to FDA	Manufacturer's No. Report 2010121220 Follow-up 2010173209 Follow-up
3/1/2011	Submission to FDA	Manufacturer's No. Report 2011034953 Initial
3/2/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. Mekhail, MD for his IND submission
3/3/2011	Submission to FDA	Manufacturer's No. Report 2011019373 Follow-up 2010103548 Follow-up
3/10/2010	Submission to FDA	Annual Report pursuant to 21 C.F.R. 312.33
3/10/2011	Submission to FDA	Manufacturer's No. Report 2011022304 Follow-up, 2011022308 Follow-up, 2010178827 Follow-up, 2011034953 Follow-up
3/11/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. Patel, MD for his IND submission
3/14/2011	Submission to FDA	Manufacturer's No. Report 2010121220 Follow-up, 2010078550 Follow-up, 2011034953 Folow-up, 2010014601 Follow-up
3/17/2011	Submission to FDA	Manufacturer's No. Report 2011019373 Follow-up, 2010097517 Follow-up, 2011034953 Follow-up

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3/21/2011	Submission to FDA	General Correspondence - Authorizing FDA to Cross Reference Pfizer IND 73,544 on behalf of Dr. Camidge, MD for his IND submission
3/30/2011	Submission to FDA	NDA 202570 – Third wave
3/31/2011	Submission to FDA	NDA 202570 - Request for Reconsideration of Trade Name
4/13/2011	Submission to FDA	NDA 202570 - Response to FDA Query on 08Apr11
4/15/2011	Submission to FDA	NDA 202570 - Response to FDA Request for information
4/15/2011	Letter from FDA	NDA Acknowledgement
4/26/2011	Submission to FDA	NDA 202570 – Amendment (Clinical)
5/03/2011	Submission to FDA	NDA 202570 – Amendment (Clinical)
5/12/2011	Email from FDA	NDA 202570 Clin Pharm comments & Analysis
5/16/2011	Email from FDA	NDA 202570 – No issues letter
5/16/2011	Email from FDA	Information request
5/19/2011	Submission to FDA	NDA 202570 – Quality Response to FDA Request 05May2011 - Establishment Description
5/24/2011	Submission to FDA	NDA 202570 – Response to FDA Query on 16May2011
5/26/2011	Submission to FDA	NDA 202570 - Amendment (Clinical), Amendment (Labeling and Packaging)
5/27/2011	Email from FDA	Convey official meeting minutes from the clinical pharmacology meeting that occurred on May 19, 2011
6/01/2011	Submission to FDA	NDA 202570 - Response to 01Jun2011 FDA Query
6/01/2011	Email from FDA	Email from FDA Requesting Dataset
6/06/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Response to FDA - Response to 01Jun2011 FDA Query
6/08/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Studies, Response to FDA - Response to 12May2011, 16May2011, 01Jun2011 and 03Jun2011 Queries
6/08/2011	Submission to FDA	Protocol Amendment - New Investigators, Protocol Amendment - Revised 1572
6/09/2011	Submission to FDA	Response to FDA CDER Query Made 02June2011 and 07June2011
6/09/2011	Submission to FDA	IND Safety Report - Safety Report (2011115014-7 day)

Date	Activity	Comments
6/13/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Response to 02June2011 FDA Query
6/15/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Studies, Response to 12May2011 FDA Query
6/17/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Response #2 to 16May2011 FDA Query
6/20/2011	Submission to FDA	Information Amendment - Clinical Information on study A8081006
6/23/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Response to FDA Queries (01Jun and 21Jun) - 23June2011
6/23/2011	Submission to FDA	IND Safety Report - Safety Report -Study A8081005 - (2011113184-Initial)
6/24/2011	Submission to FDA	NDA 202570 - Amendment - Clinical, Response to FDA Request for Information
6/28/2011	Submission to FDA	NDA 202570 - Proposed Promotional Materials
6/29/2011	Submission to FDA	NDA 202570 - Amendment – CMC, Drug Product 9 month Stability
6/30/2011	Submission to FDA	Proposed Pediatric Study Request
6/30/2011	Submission to FDA	NDA 202570 - Information Amendment - CMC Amendment
7/01/2011	Submission to FDA	NDA 202570 - Response to FDA 16 May 2011 Query
7/06/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
7/06/2011	Submission to FDA	Protocol Amendment - New Investigators, Protocol Amendment - Revised 1572 form
7/07/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
7/12/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
7/12/2011	Submission to FDA	Studies, IND Safety Report
7/13/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
7/13/2011	Submission to FDA	NDA 202570 - Amendment - Labeling and Packaging
7/15/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
7/20/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information - CMC
7/21/2011	Submission to FDA	NDA 202570 - Information Amendment - Clinical - CSR A8081018
7/22/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information

Date	Activity	Comments
7/26/2011	Submission to FDA	NDA 202570 - Amendment – Clinical, Response to FDA Request for Information - A8081009 CSR Erratum
7/27/2011	Submission to FDA	NDA 202570 - Amendment - CMC, Response to Request for Information
7/27/2011	Submission to FDA	PROPOSED PEDIATRIC STUDY REQUEST
7/29/2011	Submission to FDA	NDA 202570 - Amendment – CMC, Response to FDA queries July 25, 26, 28, 2011
8/01/2011	Submission to FDA	NDA 202570 - Amendment - Other 0034 - Response to FDA Query 22July2011]
8/01/2011	Submission to FDA	IND Safety Report (2011019373-fu8, 2011141030)
8/02/2011	Submission to FDA	NDA 202570 - Response to FDA query made 6 July Follow Up and 28 July 2011
8/03/2011	Submission to FDA	NDA 202570 - Amendment – Clinical, Response to FDA Queries [01Aug Label, 01Aug Draft PMR and 02Aug]
8/05/2011	Submission to FDA	NDA 202570 - Amendment – Clinical, Response to FDA Query [01Aug2011]
8/05/2011	Submission to FDA	Protocol Amendment - New Investigators
8/08/2011	Submission to FDA	NDA 202570 - Amendment - Response to FDA Query 05Jul2011 - Follow-up #2
8/10/2011	Submission to FDA	NDA 202570 - CMC – Pfizer response to feedback from FDA regarding Pfizer's proposal of revising the Xalkori (crizotinib) container labels post launch
8/10/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
8/11/2011	Submission to FDA	NDA 202570 - Proposed Promotional Materials: Consumer
8/11/2011	Submission to FDA	NDA 202570 - Proposed Promotional Materials: Professional
8/11/2011	Submission to FDA	NDA 202570 - Response to FDA Request for Information
8/12/2011	Submission to FDA	NDA 202570 - Amendment - Labeling Amendment and Response to FDA Request for Information
8/15/2011	Submission to FDA	NDA 202570 - Response to FDA query made on 12 Aug 2011
8/26/2011	Letter from FDA	NDA 202570 Approval letter